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CONSTABLE, LONDON.

ON PHARMACO-THERAPY AND PREVENTIVE INOCULATION

APPLIED TO

PNEUMONIA IN THE AFRICAN NATIVE

WITH A DISCOURSE ON THE

Logical Methods which ought to be Employed in the Evaluation of Therapeutic Agents

BY

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LONDON
CONSTABLE AND COMPANY LTD.
1914

ERRATA

Page 12, six lines from bottom, for "more than five times as many microbes," read "more than one hundred and twenty-five times."

Page 50, Table I, Column 1, for "390," read "380."

Page 81, Table X, Observation 2, Column 2, line 1, for "68," read "1·68" *sic.*

PREFACE

THIS book consists of a Report to the Witwatersrand Native Labour Association upon a research which was undertaken under their auspices and was directed to the discovery of some method of mitigating the ravages of pneumonia among the Native Labourers employed on the Rand Mines.

The research was carried out by the Author conjointly with Drs. W. Parry Morgan, L. Colebrook, and R. W. Dodgson; and was originally published in *The Lancet*, Part I on December 14th and 21st, 1912; Part II on January 3rd and 10th, 1914.

The task we set ourselves was to work out and put to the proof a system of preventive inoculation against pneumonia; and to ascertain what kind of resources for the treatment of pneumonia lie at disposal in *pharmaco-therapy* and *vaccine-therapy*.

We aspired to lay in connexion with each of these measures first a foundation of crucial laboratory experiments.

In *pharmaco-therapy* it seemed to us before everything else necessary to ascertain whether the drugs which were in use, or were proposed for use as bactericidal agents, exerted a bactericidal effect in the serum, and whether when administered to the patient they were actually operative in his circulating blood.

In like manner in *preventive and therapeutic inoculation* it seemed to us an initial requirement to find out whether the inoculation of our vaccines was responded

to by a definite increase in the antibacterial powers of the blood.

But here certain more fundamental problems insistently presented themselves. We found ourselves at every moment confronted with the question as to whether vaccines must undergo chemical transformation in the body before they can come into operation ; as to whether there is, when large doses of vaccine are administered, a limit to the amount which comes into operation ; as to whether the immunising responses occur at the site of inoculation or elsewhere in the body ; and as to whether there is any difference in this respect according as small or large doses of vaccine are incorporated.

I have, though these questions cannot yet be attacked by experimental methods, brought them in this Report before the reader. For from the proposing of questions comes meditation ; and from meditation the formulation of mental pictures ; and from these in the end the illuminating experiment.

Passing from the crucial experiments of the laboratory and from these problems to those which arise in connexion with the application of therapeutic measures in the field of practice, I begin by considering how conclusions can be won from cumulative experiments.

And here I show that we have at disposal two methods of procedure: the *statistical method ;* and that which I call the *experiential method*, or the *method of diacritical judgment*. And I believe I make good that this latter is logically justified ; and that it ought not, either in medicine or those other sciences which are based upon cumulative experiments, to be supplanted by the statistical method.

This critical discursus leads up to an account of the test experiments which we made, and to an exploitation

of the aforesaid methods of evaluation. I employ the *experiential method* in evaluating a short series of experiments made with pharmaco-therapy in pneumonia; and the *statistical method* in evaluating the mass-experiments made with vaccine-therapy and preventive inoculation against pneumonia.

It will be gathered from the above that I have in this Report sought, not only to make a contribution to the resolution of the problem of Pneumonia on the Rand, but also to furnish a paradigm which should exhibit the procedure to be followed in therapeutic research.

A. E. W.

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PART I

On the Pharmaco-therapy of Pneumococcus Infections; and on the Methods by which such Therapeutic Problems ought to be Investigated

I HAVE divided this Report into two parts. In *Part I* I deal with the Pharmaco-therapy of Pneumonia. In the *first Section* I consider what are the chemical properties which are indispensably necessary to the efficacy of drugs which are administered with intent to destroy the causal agents of disease in the infected body. I then enquire whether the various pharmacological agents which have been employed or proposed for employment in pneumonia possess these properties; and I bring out the fact that among the agents which we investigated æthylhydrocupreinhydrochlorate is the only one which satisfies these *a priori* requirements. In *Section II* I discuss at some length the methods by which we may evaluate the practical efficacy of therapeutic agents, and in *Section III* I bring into application the method of experiential evaluation, and endeavour to appraise the practical value of æthylhydrocupreinhydrochlorate in the treatment of pneumonia.

I reserve for Part II of this Report (*a*) the account of the work undertaken to determine the nature of the infective agent of the pneumonia on the Rand, and to lay, if such should prove possible, scientific foundations for the dosage of prophylactic and therapeutic inoculations of vaccines; and (*b*) the account of the results which have been obtained by the application of such inoculations.

SECTION I

GENERAL PRINCIPLES OF CHEMO-THERAPY AND PHARMACO-THERAPY AND PRELIMINARY INVESTIGATIONS OF THE PROPERTIES OF ÆTHYL-HYDROCUPREINHYDROCHLORATE

The discussion of the pharmaco-therapy of pneumonia may conveniently be introduced by certain general considerations with regard to the therapeutics of bacterial disease.

Here the problem which ranks before every other is that of compassing the destruction of microbes in the tissues and fluids of the living body.

Such destruction can be compassed only by bringing to bear upon the infecting microbes chemical agents which are *bacteriotropic*—i.e. which will *turn towards*, combine with, and disorganise the protoplasm of the bacteria. But it would not suffice that the chemical agents which are administered should be bacteriotropic. Our chemical agents must—and I here again employ technical terms which were coined by me in a die furnished by Ehrlich—also be *mono-tropic* for bacterial protoplasm, i.e. they must have a specific affinity for the protoplasm of the particular offending microbe, and be inert with respect to all the chemical constituents of the normal body. For if our chemical agents were *poly-tropic*, their energy would be wastefully and harmfully expended: wastefully, because they would become inert with respect to the microbes; and harmfully, because, as Ehrlich has taught us, foreign chemical substances which combine with elements of the living body act *eo ipso* as poisons—throwing out of gear the chemical metabolism and physiological functioning of any element of the body to which they may attach themselves.

Our prospects in the matter of the treatment of a bacterial infection like pneumonia will plainly depend primarily upon whether we can, or cannot, come by

chemical agents which are monotropic, or as nearly as possible monotropic, for the protoplasm of the pneumococcus, which is, in the Transvaal, as elsewhere, the causal agent of the disease.

'The outlook is as follows : In the first place the animal organism—and the human organism, it would appear, in a paramount degree—is capable of elaborating chemical agents such as we required. There is within the human body a laboratory which can, within certain limits, furnish bacteriotropic substances which will enter into destructive chemical combination with any and every variety of bacterial protoplasm. And the bacteriotropic substances of its furnishing are such as do not become inert in the blood, and such as do not poison the tissues. Upon these facts, and upon the fact that the chemical machinery which elaborates bacteriotropic substances is set in motion whenever a chemical attack is made upon the tissues by dissolved bacterial protoplasm, all *immuno-therapy*, and in particular all *vaccine therapy*, has been built up.

But we can conceive also of other chemical agency for killing microbes in the body. It is conceivable that drugs might be found which should fulfil the required condition of being monotropic for a particular variety of bacterial protoplasm, or for bacterial protoplasm in general. As already indicated, it is with the therapeutic method which proposes to employ such drugs—the *specific chemotherapy of Ehrlich*—that we are here concerned.

In connexion with this we have here to ask ourselves :—

(*a*) *Whether we do well to employ the term "chemotherapy" to denote the treatment of microbial diseases by drugs which are monotropic for the offending microbes ;*

(*b*) *What is the relation in which this method stands to traditionary medicine ;*

And (*c*) *whether it is a defensible proceeding to administer a drug where we have neither* a priori *grounds for believing that that drug could, or satisfactory evidence to show that it does, effect what it is intended to effect.*

When we have settled these preliminary questions, we shall have to ask ourselves, more particularly in connexion with æthylhydrocupreinhydrochlorate—a drug which Professor Morgenroth[1] has recently brought forward for trial in pneumonia—*in the first place*, how a favourable presumption such as will warrant our experimenting with it on man ; and *in the second place*, how a definite verdict with regard to its efficacy or otherwise in human pneumonia, can be arrived at.

(*a*) Addressing ourselves first to the question of nomenclature, let us note that *chemo-therapy* is a term which ought, in view of its etymology, to cover, in addition to specific drug treatment, also all forms of immuno-therapy, inasmuch as the attack which is made upon the microbes is, also in immuno-therapy, a chemical attack. To restrict the application of the term to specific treatment by drugs, and to set *chemo-therapy* over against *immuno-therapy* is, therefore, to suggest a quite wrong mental picture of the last mentioned. A logical terminology would employ chemo-therapy only as a generic term—classifying under it *pharmaco-therapy* or specific pharmaco-therapy—the method which employs drugs which are monotropic for the offending microbe ; and *immuno-therapy*—the method which employs bacteriotropic substances elaborated by the immunising responses of the inoculated organism.

(*b*) The possibility that the use of the term pharmaco-therapy might carry with it the suggestion that we are here reverting to the traditionary method of medicine brings up for discussion our second issue—the issue as to the relation in which the pharmaco-therapy of Ehrlich stands to the prescribing of antiseptics. It need hardly be pointed out that there is between these two a great gulf fixed. For it never entered into the conceptions of

[1] Morgenroth and Levy, " Chemotherapie der Pneumokokkeninfektion," *Berliner klin. Wochenschr.*, 1911, No. 34, and 1911, No. 44 ; Morgenroth and Rosenthal, " Chemotherapeutische Beobachtungen," *Berliner klin. Wochenschr.*, 1911, No. 3.

the physician who prescribed antiseptics to require of these that they should be monotropic for the causal agents of disease ; nor did he appreciate that the effective dose of a therapeutic agent is capable of being determined by blood tests ; nor, again, does he seem to have appreciated that there devolved upon him, once he involved himself in experimentation, a duty to set to work to ascertain the results of his experiments. He seems to have proceeded upon the assumption that any antiseptic, such as creosote, given in such doses as the patient could tolerate, must exert a check upon the growth of microbes in the body ; and he was satisfied not only himself to proceed upon that faith, but to hand it down as dogma to future generations, until it perhaps might, in the fullness of time, ultimately appear whether any good had really come of the treatment. Such, it will be recognised, is the spirit in which antiseptics were prescribed in bacterial diseases.

(*c*) Our next issue is whether it is a defensible proceeding to administer a drug concerning which we have neither *a priori* grounds for believing that it will, nor evidence to show that it does, do what is intended.

Such practice is, from the standpoint of strict science, clearly indefensible ; and we, as a profession, in point of fact, regard it as indefensible. For we reprobate in quackery, not only the fact that it has a low standard of financial rectitude, and that it proclaims its merits in public places, but also the fact that it proceeds upon assumptions which are either demonstrably false, or scientifically unjustified. And I would here emphasise that we condemn not only treatment which is based upon notoriously erroneous assumptions, but also treatment which is simple random experimentation.

Now if this is so, and if such treatment as the administration of gold as a cure for dipsomania, or of sarsaparilla as a cure for phthisis, falls under our censure as being at best mere random experimentation, and random

experimentation which is, so far as we know, unjustified by results, it is clear that such treatment as the giving of quinine in Malta fever and typhoid fever, and of salicylate of soda in streptococcal endocarditis must also fall under our censure—unless, of course, it should appear either that these drugs may be expected to kill the microbes of these diseases in the interior of the body, or that, failing this, they can be shown to be in some other way definitely useful.

In connexion with the treatment of bacterial disease we ought long ago to have verified our premisses, and to have found out whether the agents which we prescribe for the purpose of killing microbes are effective under the conditions in which they have to do their work in the body. The methods are available.

In the case of such a drug as æthylhydrocuprein-hydrochlorate—the drug which we propose here to investigate—we ought to undertake first some such series of preliminary investigations as the following :—

(1) *Measurement of the bactericidal effect exerted upon the pneumococcus by graduated dilutions of the drug in water and serum respectively.*

(2) *Prophylactic and therapeutic experiments on animals supplemented by measurement of the bactericidal effect exerted upon the pneumococcus by the blood of these animals drawn off before and after the administration of the drug.*

(3) *Preliminary experiments on normal and infected men, supplemented by measurements of the bactericidal effect exerted upon the pneumococcus by the blood of these men drawn off before and after the administration of the drug.*

(1) MEASUREMENT OF THE BACTERICIDAL EFFECT WHICH IS EXERTED IN VITRO BY GRADUATED DILUTIONS OF THE DRUG IN WATER AND HUMAN SERUM RESPECTIVELY.

The object of such experiments is to determine (*a*) whether the chemical energy of the drug is expended

wastefully upon the blood fluids; (*b*) to determine, with a view to fixing the dose, what concentration of the drug will be required to exert a bactericidal effect in the blood; and (*c*) whether the introduction of the antiseptic into the blood interferes with phagocytosis or any other of the antibacterial properties of the blood.

The experiments which are here subjoined, and which were conducted with a modification of the technique which I have elsewhere[1] described, bring out very clearly that, while our ordinary antiseptics are polytropic and expend their energy wastefully upon the blood fluids, we have in æthylhydrocupreinhydrochlorate a chemical agent which exerts its effect practically undiminished in serum. The experiments bring out that dilutions of 1 part of lysol in 500 parts of serum, dilutions of 1 part of creosote in 2500 to 12,500 parts of serum, and dilutions of 1 part of guaiacol in 2500 parts of serum fail to kill the pneumococcus; while dilutions of 1 part of lysol in 62,500 parts of water, dilutions of 1 part of creosote in 300,000 of water, and dilutions of 1 part of guaiacol in 1,500,000 of water, all kill the pneumococcus. They bring out further that dilutions of 1 part of æthylhydrocupreinhydrochlorate in 400,000 parts of serum kill the pneumococcus, and that dilutions of 1 in 800,000 inhibit the growth; and that the antiseptic values of the serum dilutions of the drug do not differ appreciably from the values obtained for watery solutions. Finally they show that æthylhydrocupreinhydrochlorate exerts its bactericidal effect specifically upon the pneumococcus.

[1] For the general method see Wright, *Technique of the Teat and the Capillary Glass Tube* (Constable, London, 1912), pp. 108–113.

The modification here employed consisted in using, instead of a unit volume of the bactericidal agent and an aliquot unit volume of microbial suspension, a 5 c.mm. volume of the bactericidal agent, measured by the aid of a mark placed upon the stem of the pipette, and only so much of the bacterial suspension as was obtained by filling to this mark and blowing out again. The number of microbes which this *priming* furnished was elicited in graduated dilutions of the bacterial suspension by taking a series of eight or more control tubes, filling these in, after priming, with serum broth, and then cultivating at 37° C. *Vide* also *infra*, pp. 61–62.

Measurement of the bactericidal effect exerted upon the pneumococcus by lysol in graduated dilutions made with water and human serum[1] respectively.

Strength of the lysol dilutions which were brought in contact with the pneumococci (in each case 5 c.mm. of the lysol dilution was digested overnight with several thousands of pneumococci).

	$\frac{1}{500}$	$\frac{1}{2500}$	$\frac{1}{12500}$	$\frac{1}{62500}$	$\frac{1}{312500}$	$\frac{1}{1562500}$
Dilution in water	0	0	0	0	×	×
„ human serum..	×	×	×	×	×	×

The signs 0 and × respectively are employed to signify that a growth was not, or was, obtained on cultivating in serum both the microbes which had been digested with the bactericidal agent.

Measurement of the bactericidal effect exerted upon the pneumococcus by creosote in graduated dilutions made with 0·85 *per cent salt solution and human serum respectively.*

Strength of the creosote dilutions which were brought in contact with the pneumococci (in each case 5 c.mm. of the creosote dilution was digested overnight with about 625 pneumococci).

	$\frac{1}{500}$	$\frac{1}{2500}$	$\frac{1}{12500}$	$\frac{1}{62500}$	$\frac{1}{312500}$
Dilution in NaCl 0·85 per cent ..	0	0	0	0	0
„ human serum	0	×	×	×	×

Strength of the creosote dilutions which were brought in contact with the pneumococci (in each case 5 c.mm. of the creosote dilution was digested with about 45,000 pneumococci).

	$\frac{1}{500}$	$\frac{1}{2500}$	$\frac{1}{12500}$	$\frac{1}{62500}$	$\frac{1}{312500}$
Dilution in water	0	0	0	0	0
„ human serum ..	0	0	×	×	×

Measurement of the bactericidal effect exerted upon the pneumococcus by guaiacol in graduated dilutions made with water and human serum respectively.

Strength of the guaiacol dilutions which were brought in contact with the pneumococci (in each case 5 c.mm. of the guaiacol dilution was digested overnight with about 45,000 pneumococci).

	$\frac{1}{500}$	$\frac{1}{2500}$	$\frac{1}{12500}$	$\frac{1}{62500}$	$\frac{1}{312500}$	$\frac{1}{1562500}$
Dilution in water	0	0	0	0	0	0
„ human serum ..	0	×	×	×	×	×

[1] The human sera which were employed in this and the following experiments exerted no bactericidal effect on the pneumococcus.

Measurement of the bactericidal effect exerted upon the pneumococcus by æthylhydrocupreinhydrochlorate in graduated dilutions made with 0·85 *per cent NaCl and human serum respectively.*

Strength of the æthylhydrocupreinhydrochlorate dilutions which were brought in contact with the pneumococci (in each case 5 c.mm. of the æthylhydrocuprein dilution was digested overnight with several thousands of pneumococci).

	$\frac{1}{1000}$	$\frac{1}{10000}$	$\frac{1}{50000}$	$\frac{1}{100000}$	$\frac{1}{200000}$	$\frac{1}{400000}$	$\frac{1}{800000}$
Dilution in NaCl 0·85 per cent	0	0	0	0	0	0	0
Dilution in human serum	0	0	0	0	0	0	×[1]

Note.—A control in which the same number of pneumococci were introduced into 5 c.mm. of untreated normal human serum gave a plentiful culture of pneumococci.

Measurement of the comparative bactericidal effects of serum dilutions of æthylhydrocupreinhydrochlorate upon pneumococcus and staphylococcus, and pneumococcus and Bacillus para-typhosus respectively.

Strength of the dilutions of æthylhydrocupreinhydrochlorate in serum which were brought into contact with the bacteria (in each case 5 c.mm. of the æthylhydrocupreinhydrochlorate dilution was digested overnight with some thousands of microbes).

	$\frac{1}{100}$	$\frac{1}{1000}$	$\frac{1}{5000}$	$\frac{1}{10000}$	$\frac{1}{15000}$	$\frac{1}{20000}$	$\frac{1}{25000}$	$\frac{1}{40000}$
Staphylococcus	—	—	×	×	×	×	—	—
Pneumococcus	0	0	0	0	0	0	0	0

	$\frac{1}{200}$	$\frac{1}{1000}$	$\frac{1}{10000}$	$\frac{1}{20000}$	$\frac{1}{40000}$	$\frac{1}{60000}$	$\frac{1}{80000}$	$\frac{1}{100000}$
Bacillus para-typhosus	×	×	×	×	×	×	×	×
Pneumococcus	—	—	0	0	0	0	0	0

Note.—In each case a control in which the same number of pneumococci were introduced into 5 c.mm. of untreated normal serum gave a plentiful culture of pneumococci.

It is clear upon the basis of these experiments that we may reasonably infer that æthylhydrocupreinhydrochlorate would be capable of exerting a bactericidal action upon the pneumococcus *in vivo*. Further, if we work upon the figures of these experiments, upon the assumption that we are dealing with a man of 70 kilos

[1] Very sparse culture after thirty-six hours.

(of which 7 kilos would represent blood), and on the quite unrealisable assumption that when a drug is administered the whole quantum will be absorbed into the blood and come into operation at the same moment, the doses of the various antiseptics which would be requisite to produce a bactericidal effect upon the pneumococcus circulating in a patient's blood can be calculated. The dose in the case of lysol would be greater (experiment does not tell us how much greater) than 14 grm. ($\frac{1}{2}$ oz.); in the case of creosote and guaiacol greater than 2·8 grm. (over 45 minims); and of Morgenroth's drug only 0·017 grm.

(2) PROPHYLACTIC AND THERAPEUTIC EXPERIMENTS UPON ANIMALS INOCULATED WITH THE PNEUMOCOCCUS SUPPLEMENTED BY IN VITRO EXAMINATIONS OF THEIR BLOOD DRAWN OFF BEFORE AND AFTER THE ADMINISTRATION OF THE DRUG.

While *in vitro* experiments such as the above will tell us whether the chemical energy of a bactericidal agent is, or is not, wastefully expended upon the blood fluids, and what is the minimum quantity of the drug that must be introduced into those fluids in order to achieve a bactericidal effect, they cannot tell us whether the drug will prevent or cure an infection, and whether the drug will exert a poisonous action upon some important element of the animal machinery. Experiments *in vivo* are here required.

But too high a value may be set upon purely *in vivo* experiments. It is in the laboratory often forgotten that animal experiments, when not followed up by blood tests conducted *in vitro,* leave us quite in the dark as to the causes of the observed effects. For instance, in the case where infecting bacteria have been killed by the administration of a bacteriotropic drug, they leave unresolved the question whether this result is to be ascribed wholly

to the drug, or in part to the drug and in part to superadded immunising responses. Again it is often forgotten that the conditions in the human organism may be fundamentally different from those in the animal with respect to the form which the bacterial infection takes, the access of the blood fluids to the infecting microbes, the absorption and excretion of the drug, and the susceptibility of the nobler tissues to its toxic action.

These points having been premised, we may turn first to the consideration of the results of the animal experiments which were carried out by Morgenroth and his fellow-workers. These experiments are destined to stand out as a landmark in the history of the pharmaco-therapy, because they furnish the first demonstration of the possibility of preventing and curing a bacterial—as distinguished from a protozoal or spirochætal—infection by the administration of a drug. All that it will be necessary to do here will be to give the general result of Morgenroth's experiments. These were conducted on mice inoculated with cultures of pneumococcus which killed without exception every untreated mouse. The æthylhydrocupreinhydrochlorate or sulphate was administered in some cases before, in others after, the inoculation. Employed thus the drug prevented the development of the infection in some 90 per cent of the prophylactically treated; and cured about 50 per cent of the animals in which treatment was postponed till after inoculation. To the clear and complete evidence which Morgenroth's tabulated experiments furnish upon these points, there remained only to add bactericidal experiments conducted *in vitro* on the blood fluids and urine of treated and untreated mice. Subjoined will be found details of such bactericidal experiments undertaken by us upon untreated mice and mice treated with the same doses of æthylhydrocupreinhydrochlorate as were employed by Morgenroth in his experiments.

Measurement of the bactericidal effect exerted upon an enumerated suspension of pneumococcus by (a) *the undiluted pooled serum of a group of mice treated with æthylhydrocupreinhydrochlorate* (2 *mgrm. to* 10 *grm. body-weight*), *and* (b) *by the undiluted pooled serum of a control group of untreated mice.*

							Bactericidal effect calculated out for 1 c.c. of serum
Dilutions of the pneumococcus suspension which were employed	$\frac{1}{1}$	$\frac{1}{5}$	$\frac{1}{15}$	$\frac{1}{45}$	$\frac{1}{135}$	$\frac{1}{405}$	
Pooled serum of five untreated mice	×	×	×	×	×	×	1 c.c. serum kills 0 cocci
Pooled serum of five treated mice three hours after subcutaneous injection of the drug	×	×	×	0	0	0	1 c.c. serum kills 1200 cocci
	$\frac{1}{1}$	$\frac{1}{4}$	$\frac{1}{16}$	$\frac{1}{64}$	$\frac{1}{256}$	$\frac{1}{512}$	
Pooled serum of four untreated normal mice	—	×	×	×	×	×	1 c.c. serum kills 0 cocci
Pooled serum of four treated mice three hours after injection of the drug	×	×	×	0	0	—	1 c.c. serum kills 1,600 cocci.

Measurement of the bactericidal effect exerted upon an unenumerated suspension of pneumococcus by (a) *the undiluted pooled serum and pooled urine of a group of mice treated with æthylhydrocupreinhydrochlorate* (2 *mgrm. to* 10 *grm. body-weight*), *and* (b) *by the undiluted pooled serum and the pooled urine of a control group of untreated mice.*

Dilutions of the pneumococcus suspension which were employed	$\frac{1}{5}$	$\frac{1}{25}$	$\frac{1}{125}$	$\frac{1}{625}$	$\frac{1}{3125}$	
Pooled serum of four untreated mice	—	—	×	×	0	
Pooled serum of four treated mice killed five hours after subcutaneous injection of the drug	0	0	0	0	0	The serum of the treated killed more than twenty-five times as many pneumococci as the serum of the untreated mice
Pooled urine of four untreated mice	—	×	×	×	0	The urine of the treated killed more than five
Pooled urine of four treated mice	0	0	0	0	0	times as many microbes as the urine of the untreated mice

We have here, in the data with regard to the sera of mice treated with æthylhydrocupreinhydrochlorate, satis-

one hundred & twenty

factory explanation of the successful results obtained by Morgenroth in his experiments upon animals. Further, we have in the data which refer to the urine of the treated mice ; in those afterwards obtained in experiments made on the urine of man ; and also in the fact that the bactericidal power which the serum acquires after the exhibition of Morgenroth's drug is not diminished by heating to 60° C. satisfactory evidence that the bactericidal effects recorded above are due to the absorption of the drug into the blood fluids and to its excretion in the urine.

(3) PRELIMINARY EXPERIMENTS ON UNINFECTED OR INFECTED MEN SUPPLEMENTED BY EXPERIMENTS UPON THEIR BLOOD DRAWN OFF BEFORE AND AFTER THE ADMINISTRATION OF THE DRUG.

The purport of these experiments upon man is to test the inferences drawn from the *in vitro* experiments on human blood which have been described under (1), and from the *in vivo and in vitro* experiments on animals which have been described under (2). The ideal order of experimentation is to commence with experiments on normal men : *first*, because it would be to the advantage of the sick that we should, when dealing with them, have something to guide us in our dosage and the interspacing of our doses ; *secondly*, because we may reasonably hope to obtain from normal men timelier warning of any toxic effect that might be produced by our drug.

The experiments which are subjoined were carried out in part upon normal men and in part upon pneumonia patients ; and we may in this particular section confine ourselves to the issue as to whether, under the administration of the drug, the blood fluids of the patient acquire a bactericidal power, or alter with respect to their opsonic power. And we may leave over to Section III the issue as to whether the exhibition of the drug exerts a favourable influence on the course of pneumonia.

Measurements of the bactericidal and opsonic power exerted upon the pneumococcus by human serum drawn off before and after the administration of æthylhydrocupreinhydrochlorate.

Experiment No. I.—(*a*) Three normal natives receive on January 31, 1912, 0·5 grm. of Morgenroth's drug by the mouth.

Dilutions of the pneumococcus suspension which were employed		$\frac{1}{25}$	$\frac{1}{75}$	$\frac{1}{225}$	$\frac{1}{675}$	$\frac{1}{2025}$	Bactericidal effect exerted by 5 c.mm. of serum	Opsonic index
Approximate number of pneumococci in the quantum of suspension employed		54	18	6	2	$\frac{2}{3}$		
No. 106,603	Before administration	×	×	0	0	0	Kills 6 pneumococci	0·27
	Three hours after administration	0	0	0	0	0	Kills 54 pneumococci or more	0·36
No. 79,519	Before administration	×	0	×	×	×	Kills 0 pneumococci	0·22
	Three hours after administration	0	0	0	0	0	Kills 54 pneumococci or more	0·38
No. 106,717	Before administration	×	×	×	×	0	Kills 0 pneumococci	0·30
	Three hours after administration	0	0	0	0	0	Kills 54 pneumococci or more	0·42

(*b*) The same three men receive on February 1, 1912, 1 grm. of Morgenroth's drug by the mouth, and blood specimens are taken three hours after.

Dilutions of the pneumococcus suspension which were employed	$\frac{1}{5}$	$\frac{1}{15}$	$\frac{1}{45}$	$\frac{1}{135}$	$\frac{1}{405}$	Bactericidal effect of 5 c.mm. of serum	Opsonic index
Approximate number of pneumococci in the quantum of suspension employed	54	18	6	2	$\frac{2}{3}$		
No. 106,603	×	×	×	×	×	Kills 0 pneumococci	0·34
No. 79,519..	0	0	0	0	0	Kills 54 pneumococci or more	0·24
No. 106,717	×	×	0	0	0	Kills 6 pneumococci	0·37

Experiment No. II.—Normal natives Nos. 1 and 2 receive 1 grm., and Nos. 3 and 4 0·5 grm. of Morgenroth's drug by the mouth. Comparative determinations of the bactericidal power of their sera before, and three hours after the administration of the drug show, in the case of No. 1 : before administration, no inhibiting or bactericidal effect ; after administration, a bactericidal power of over 35 pneumococci per 5 c.mm. Similar estimations in the case of Nos. 2, 3, and 4 show : before administration, no inhibiting or bactericidal effect ; after administration, no bactericidal effect but inhibition of growth in all dilutions. Opsonic measurements carried out on these bloods gave the following results :—

	Pneumococcus (*phagocytic counts*)		Staphylococcus (*phagocytic counts*)	
No.	Before administration	After administration	Before administration	After administration
1	2·12	1·94	1·02	1·29
2	3·34	2·94	1·51	1·78
3	2·0	2·14	1·9	1·93
4	1·76	2·36	1·59	1·24

There was ground, both in this experiment and the next, for suspecting that one, or perhaps two, of the natives may have found opportunity to vomit the drug.

Experiment No. III.—Three normal natives receive 0·5 grm. of Morgenroth's drug by the mouth. Comparative determinations of the bactericidal power of their sera before, and three hours after the administration of the drug show, in the case of Nos. 1, 2, and 3 : no bactericidal effect before administration ; in the case of Nos. 1 and 3 : no bactericidal effect after administration ; in the case of No. 2 : after administration, a bactericidal effect of 32 pneumococci per 5 c.mm.

Experiment No. IV.—A native with pneumonia receives 0·5 grm. of Morgenroth's drug hypodermically, and 0·5 grm. at the same time by the mouth, and samples of his blood are taken for bactericidal measurement before and three hours after the administration of the drug.

							Bactericidal effect of 5 c.mm. of serum
Dilutions of the pneumococcus suspension which were employed		$\frac{1}{5}$	$\frac{1}{25}$	$\frac{1}{125}$	$\frac{1}{625}$	$\frac{1}{3125}$	
Approximate number of pneumococci in the quantum of suspension employed		3125	625	175	25	5 or more	—
Patient 60847	Before administration	×	×	×	×	×	Kills 3125 pneumococci or more
	After administration	0	0	0	×	0	

Experiment No. V.—Three natives with pneumonia receive Morgenroth's drug : No. 1 a dose of 1 grm. by the mouth ; No. 2 a dose of 1 grm. hypodermically, and No. 3 a dose of 0·5 grm. hypodermically.

Dilutions of the pneumococcus suspension which were employed		$\frac{1}{25}$	$\frac{1}{175}$	$\frac{1}{625}$	$\frac{1}{3125}$	Bactericidal effect exerted after administration of the drug
Patient 80199	Before administration	×	×	×	×	Serum kills more than 125 times as many pneumococci as it did before
	Five hours after administration	0	0	0	0	
Patient 60831	Before administration	×	×	×	0	Serum kills more than 25 times as many pneumococci as it did before
	Five hours after administration	0	0	0	0	
Patient 79519	Before administration	×	×	×	0	Serum kills more than 5 times as many pneumococci as it did before
	Five hours after administration	×	0	0	0	

The experiments which have been set forth above make it clear that in man as in mice—but we found that the same did not hold in rabbits—the blood is rendered bactericidal to the pneumococcus by the administration of æthylhydrocupreinhydrochlorate. It is further brought out in Experiment No. 1 and more clearly in Experiment No. 2 that the *opsonic power* of the serum is not appreciably affected by the exhibition of the drug.

SECTION II

PROBLEM AS TO WHAT LOGICAL METHODS OUGHT TO COME INTO APPLICATION IN ENQUIRIES INTO THE EFFICACY OF THERAPEUTIC AGENTS AS APPLIED IN ACTUAL PRACTICE

INTRODUCTION

In the case where any one, and *a fortiori* in the case where all, of the lines of enquiry which have been suggested create a presumption in favour of the therapeutic

efficacy of a drug, we ought to proceed to determine whether it is effective in actual application.

But when we come to issues of this kind—and precisely similar ones will present themselves in connexion with prophylactic and therapeutic inoculation—we are outside the territory in which scholastic logic applies; and are, moreover, in a territory in which the logical intuitions of mankind give only dim light. It will therefore be very well worth while to try to make clear to ourselves the logical principles which ought to rule and regulate our reasonings in the sphere of practical enquiries such as we have here in contemplation.

We may begin at the very foundation.

The raw material of science consists of *unconformable facts*. That is as much as to say that, in starting out upon any task of research, we take our departure from discordant observations which do not admit of being assembled in any general propositions.

Out of such observations scientific generalisations may be won by one or other of two procedures :—

We may proceed by the *method of crucial experimentation* (or *crucial observation apart from experiment*). That is to say, we may remove out of our way, first one complicating circumstance, and then another until we have arrived at quite perspicuously simple conditions. Experimentation will now furnish sequences of *conformable facts*. Our *substantive* experiment will give in a uniform manner a specific result. And our *control* experiment will give, as regularly, a contrasted result. And these results will be expressible in *universal propositions* which will within their range apply to every individual instance without exception.

This experimental method—it is, as the reader will recognise, the method which was brought into application in the *in vitro*, and the *in vivo and in vitro* experiments, which were set out above—is very far from being generally applicable over the whole of the territory of

knowledge. It can be applied only in those areas of the scientific field where we can by the exercise of ingenuity artificially simplify the experimental conditions.

Where there is no possible way of doing this, the method of crucial experiment must be laid aside, and the *method of cumulative experimentation* (or *cumulative observation apart from experiment*) must be brought into application. In other words, we must institute a twin series of substantive and control experiments, and collate their results.

The ordinary scientific worker will probably not have considered the mental readjustments which will be called for when he changes over from the method of crucial experiment to that of cumulative experiment.

Instead of trying vainly to find a way out of experimental complications, he now accepts them.

Instead of insisting that experimentation must bring forth conformable facts, and universal propositions, and mathematical certainty, he is now content if he can win his way to general truths.

And he must content himself with these because in a world which is infinitely intricate we can never count upon any phenomenon turning up time after time without exception; and we can never be sure that any conclusion is entitled to rank as a universal proposition until, by a process of *exhaustive sampling*, it has been shown to hold true in every possible conjuncture.

This leads up to a series of very important general considerations on the subject of certainty.

The *first* is that certainty founded upon exhaustive sampling is under actual conditions practically impossible to come by.

The *second* is that no one who could be called reasonable would, when brought up against a situation which demands practical action, ever suggest waiting for certainty.

The *third* is that certainty, supposing that it ever were

within our grasp, would furnish neither foresight of events nor practical guidance in life. It would, as a pregnant saying of Schopenhauer puts it, be "the blind man's staff without the dog: mere safe equipoise upon a position already reached."

And now as a final result of all these the question presents itself: What are we going to put in the place of that absolute certitude and of those universal propositions which have filled so large a place in our mental system?

The answer to this would appear to be as follows: The place in our system of thought which is by old prescription occupied by the conception of certainty is going to be taken over by the conception of probability. And, in all those departments of knowledge where we build upon cumulative experimentation or observation, *generic propositions*—or, as we familiarly call them, *general truths*, or *general rules*, or *generalisations*—are going to stand in the room of universal propositions.

Again, in connexion with generic propositions, there will needs have to come into application a new logic and a new technique of reasoning.

We shall have to forsake the logic of Aristotle and the Schoolmen. For this is a logic which ignores unconformable facts; and it is conversant only with that kind of general proposition which applies to every instance and every member of a class, and is therefore *ex hypothesi* contradicted and discountenanced by any exception.

We have to abandon this system of logic for a system which extends recognition to unconformable facts, and which is conversant with that kind of general proposition which regards only the ordinary case and the general rule, and so *ex hypothesi* comports with exceptions.

In summary we have to abandon a logic which is out of relation with the actual world, which makes inductions only from conformable facts, thinks in universal propositions, trafficks in fictitious certitudes, and is unfruitful; for a logic which stands in close relation with actuality,

makes inductions from unconformable facts, thinks in generic propositions, trafficks openly and avowedly in probabilities, and succeeds in turning these to practical account.

But it will not suffice to indicate in the outline only the features of that logic which will make it possible to synthesise, and educe conclusions from discordant observations. It will be necessary also to identify and subject to analysis the different logical procedures which the human mind brings into application in such reasonings; not forgetting in this connexion that the selfsame logical operations, which are applicable to the solution of the particular problems which are before us here, must be applicable over the whole range of medicine; and, indeed, must be applicable not only there, but also wherever in ordinary life we adjudicate upon anything or take practical action.

ON REASONING FROM THE UNCONFORMABLE FACTS WHICH ARE FURNISHED BY CUMULATIVE EXPERIMENTS AND OBSERVATIONS.

The data which are furnished by the method of cumulative experiment and observation may be marshalled and evaluated by one or other of two different procedures.

They may be dealt with, on the one hand, by (*a*) the *method of diacritical judgment*, or *experiential method;* and, on the other hand, (*b*) by the *statistical method.*

If we employ the *experiential method*—i.e. if we take into account the whole complex of impressions which have been left upon the mind by experience, we arrive at a *generalisation* (which is the general law or general evaluation of the class). This will express the result which we have witnessed in the majority of our cases; and it will, if our experience has been a typical one, hold good of a majority of every other series of such cases.

If, on the contrary, we proceed by the *statistical method* —i.e. if we tabulate and count up our results, we arrive at a *statistical evaluation.* This will set forth the per-

centage of cases in which a particular result was achieved ; and it will, if our experience is a typical one, give the correct odds in favour of that result reproducing itself in the case to which we are giving our attention.

An objection will already have suggested itself : " Is it," it will be asked, " beyond question that what is here " called the ' experiential method,' is properly distin- " guishable from the statistical method ? And does not " the distinction between the methods consist only in " this, that when we bring into application the " ' experiential method ' we are relying upon a badly " kept and blurred mental record of the facts which " warrants at best an evaluation in general terms, while " we have in connexion with the statistical method an " accurately kept written record which warrants an " evaluation in precise figures ? "

The question may be answered by analysing somewhat more minutely first the statistical, and then the experiential method.

Further Analysis of the Statistical Method.

The statistical method of evaluation involves three separate operations : (1) A critical study of the raw material of experience with a view to selecting a suitable criterion upon which to build up our statistics ; (2) the sifting of that raw material by aid of the criterion we have chosen ; and (3) the evaluation of the results which the sifting has yielded.

(1) *Critical Study of the Raw Material of Experience with a view to selecting a suitable Statistical Criterion.*— We here endeavour to discover in our cases a criterion upon which to build up our statistics. This criterion may be either (*a*) a really *critical feature* (the fact of escaping infection, or of recovering from an attack would, for instance, constitute such a critical feature) by reference to which our substantive and control cases can be distributed into two sharply contrasted sub-groups of

plusses and minuses, or 'yesses' and 'noes,' the individual cases being represented by a plus or a minus, or a 'yes' or a 'no,' according as they do, or do not, exhibit the critical character; or (*b*) a *feature* which is common to all the cases, which can be expressed in figures, and which *varies in a significant manner* (let us say such a feature as the number of days during which each patient's temperature has ranged above the normal).

(2) *Sifting of the Raw Material by the Aid of the Criterion we have chosen.*—The basis upon which we are to go to work having been settled, we construct upon that basis a skeleton framework for our tables, and enter each substantive and control case as it comes in its proper column, putting out of sight and regard every element in the case other than the feature we have elected to consider.

(3) *Evaluation of the Results which the Sifting has yielded.*—We count up the plusses and minuses, or 'yesses' and 'noes,' and find the relative proportion of these in our series of substantive and control cases; or, as the case may be, we total up the figures which represent the respective values of the significant feature in each individual case, and make a comparison between the totals for our two groups of cases. In either case we express the final result in the form of a percentage; and, where the occasion calls for this, compute, or have computed for us, the 'probable error' which we should be incurring if we took the substantive and control cases upon which we based our calculations as absolutely average samples of the classes they represent.

Further Analysis of the Experiential Method.

As compared with the statistical method the experiential is a much less sophisticated, and a much less arbitrary method of evaluation. When we employ it we let the two separate streams of experience which correspond to the twin series of substantive and control

experiments filter through our minds, and then compare the impressions which have been imprinted. While no complete account can be given of the psychological processes by which this comparison is carried out, the two following points may be noted.

When we bring into application the experiential method we take into consideration every feature of each case and not, as in the case of the statistical method, only one selected feature—in other words, the *experiential* is a method of *unrestricted;* the *statistical* a method of *restricted outlook.* And the mental record upon which we proceed need not be inaccurately kept or blurred. When, for instance, we obtain in a succession of consecutive cases one and the same result, each succeeding case will render more distinct the impression made by the preceding case ; and when a case which is at variance with a series of previous cases turns up, it will, by contrast, stand out very clearly in our consciousness.

Spheres of Application of the Experiential and Statistical Methods.

Neither the experiential nor the statistical method of evaluating cumulative experience is a method of universal application.

The *experiential method* will be inapplicable in the case where the substantive and control cases are distinguished by only a very small average difference. And the experiential method will be of only very limited utility in the case where we have in each of these groups a very heterogeneous assortment of cases. For we cannot, in either of these conditions, safely draw any conclusions from a small number of cases. And the capacities of the human intellect are unequal to the task of carrying in mind and weighing one against the other a long procession of substantive, and a long procession of control cases.

There attaches to the use of experiential method also

another important limitation. It is impracticable, in the case where the evaluations of different observers diverge, to bring these together into a single judgment. For there is no method for finding the resultant of a number of non-numerical evaluations.

The difficulties in connexion with the application of the *statistical method* are not less serious than those encountered in the application of the experiential method. But they are of a different order.

They lie in the fact that it is the exception to find in connexion with clinical material either a really critical feature by reference to which the cases can be sorted out into successes and failures; or a significant feature which is universally present and which lends itself to arithmetical evaluation.

The difficulty of finding a critical feature which would subserve the purposes of a statistical evaluation can be illustrated by taking the case of the treatment of phthisis. It matters not whether we take as our criterion of success, the disappearance of the tubercle bacilli from the sputum, or the disappearance of the pyrexia, or a gain in body-weight, or the return of the patient to full work, or simply the survival of the patient for a certain fixed period: no matter what criterion we elect, there will inevitably be found among those who benefit by the treatment many in whom that particular condition is not realised, and also many in whom the fulfilment of that condition will not be of critical value.

It might be suggested that these difficulties should be circumvented by allotting a certain arbitrary number of marks to each significant clinical phenomenon, and then evaluating in accordance with such convention.

In reality, such a scheme resolves itself into a proposal to make a number of separate statistical tables, and to combine the results in such a way as to make of the statistical method a method of unrestricted outlook.

This proposal would make shipwreck upon the fact

that it would be impossible to include every case in every column of such a compound statistical table (the apyrexic cases, for instance, would have to be omitted from the column relating to pyrexia). And, again, it would make shipwreck upon the fact that there would be no accepted rate of exchange at which improvement in one respect could be reckoned against improvement in another; no basis for setting off, let us say, a temporary gain in weight in one patient against a temporarily reduced pyrexia in another.

As a certain counterweight against the disadvantages we have been considering is to be reckoned the fact that, once a satisfactory basis for statistics has been found, we can obtain in the form of a single expression the resultant of the evaluations of any number of independent observers.

There is one further point to be considered under this heading; and this, properly appreciated, may legitimately, in the case where a choice has to be made between two methods of evaluation, determine our decision. When we evaluate by a method of restricted outlook, which takes into account only a single feature in each case (and we have seen that in the statistical is such a method), we must, before a trustworthy conclusion can be arrived at, pass in review a very large number of cases. When we evaluate by a method of unrestricted outlook (such as the experiential method) in which every feature in each case is taken into account, a much smaller number of cases will suffice.

When there is a shorter and a longer way it will be well not to choose, *on principle*, the longer.

Is it practicable to bring into View by the aid of the Statistical Method a small Average Difference subsisting between a Series of Substantive and a Series of Control Cases?

We have already seen that our inability to carry in

mind and evaluate such long sequences of cases as are, in the case here in question, indispensable, makes it futile to employ the experiential method for the detection of fine differences. There remains for consideration how far it will be possible to detect a small average difference between two series of cases by the aid of the statistical method. We here operate under much more favourable conditions, both in the respect that we take our cases one by one, and enter up the results as we go ; and in the respect that we can add the figures of one observer to those of another, and go on doing this indefinitely. But while the number of cases which we can thus bring under review is unlimited, real advantage accrues from this only in the case where the criterion which supplies the basis for the statistical classification is one which makes it practically impossible for mistake to creep in. Where such a criterion is not available, and where the personal judgment of the observer is called into requisition, it is very difficult for him, in going through a long series of cases, to maintain exactly the same standard of value. The observer's estimate of what amounts to an " attack " or a " relapse " or a " cure " will, for instance, vary ; and it will be impossible in the case of different observers to obtain conformity to a uniform standard. Hence, even with the statistical method it is nearly always impracticable in the case where it is a question of only a small average difference between two groups of cases to make sure that that difference actually exists.

General Considerations in Connexion with the Accuracy of the Evaluations made respectively with the Experiential and Statistical Method.

The accuracy of an evaluation of a series of cumulative experiments depends upon three factors : (i) upon the result of every case which has come under observation being brought upon the record, (ii) upon every significant element in each case being brought into account, and

(iii) upon a correct value being assigned to every such element.

It will be clear that neither the experiential nor the statistical method comes anywhere near fulfilling these conditions.

In the case of an *experiential evaluation*, the position is as follows : We have no real guarantee for the inclusion of every case in the record. On the other hand, we can feel confident that no significant factor has been excluded from consideration, and that, so far as possible, credit has been given for every such factor. Thus, for example, we may, where the recovery of a patient counts as a success, feel sure that proportionately more credit will have been allowed to a rapid and triumphant recovery ; and proportionately less to a slow and incomplete recovery.

In the case of a *statistical evaluation* the position is almost the reverse. We have here a very strong presumption—for the keeping of a statistical table affords such a presumption—that the result of every case has come upon the record. On the other hand we know that no significant element except that which serves as the basis of classification has been brought into the account. And, in the case where the presence or absence of a critical feature provides the basis of classification, we know that the evaluation is inaccurate in the respect that there has been assigned to each case, according as it fell above or below an arbitrary line, either the absolute maximum of marks, or no marks at all.

These general considerations have prepared the way for bringing forward the suggestion that the ideal of minutely accurate quantitative statement which is always floating before the vision of the statistician should in the field of clinical medicine be frankly abandoned. This would mean recognising that it is, in medicine, impossible by the method of cumulative experiments either (*a*) to detect minute differences, or (*b*) to arrive in any case at any accurate quantitative conclusions.

The frank recognition of this would, in point of fact, leave the practice of medicine practically unaffected. For, both in the case where the question arises whether we are, or are not, to apply a method of treatment which is doubtfully effective, and in the case where we have to elect between two alternative lines of treatment which are almost equally effective, it will not seriously matter what choice we make.

The suggestion that the ideal of minutely accurate evaluation should, in the field of clinical medicine, be abandoned, might, however, meet objection from a different point of view. It might be asked whether it would be possible for medicine to make progress if that ideal were abandoned. There is a very simple answer to this in the fact that whenever medicine has progressed it has progressed by making a new departure suggested by a chance observation, or based upon a crucial laboratory experiment. It has not gone forward by refining upon such discoveries by the aid of cumulative experiments. We can, therefore, well afford to let all this laborious ineffective striving after the accurate evaluation of cumulative experiments go.

Finally, it may be explained that the suggestion which is here put forward is not that all numerical evaluation should disappear from medical literature. It is that such evaluations—formulated though they be in precise figures, and corrected though they be for the probable error due to random sampling—shall not be ranked with exact scientific measurements. We shall have conceded to them their proper relative rank in science when we have put them upon a level with evaluations expressed in round numbers, and with approximative evaluations such as are obtained by the experiential method.

They must, however, from the standpoint of ethics, rank below these. For, while approximative experiential evaluations are neither more nor less than what they purport to be, a precise numerical evaluation is a con-

cession to that human weakness which insists that it must always be allowed to achieve, even at some sacrifice of truth, an absolutely definite mental image.

We shall presently have to come back upon considerations of ethics. For the moment we have to complete our study of the advantages and disadvantages which are associated with the use of the experiential and statistical methods by asking ourselves the following questions :—

Is a Greater Measure of Clinical Skill and Experience required of the Evaluator who employs the Experiential Method than of the Evaluator who employs the Statistical Method ?

It is currently believed among the laity that a medical evaluator who applies the statistical method need not possess the authoritative clinical skill and experience which would be required of an evaluator who applies the experiential method. For example, it would probably be the general opinion among laymen that special skill would have to be requisitioned to determine by the experiential method whether, let us say, pneumonia runs a milder course in the prophylactically inoculated and the treated than in the uninoculated and the untreated, but that it would be unnecessary to requisition such skill to determine, for the purpose of a statistical evaluation, whether a man falls sick of pneumonia and whether he dies of that disease.

A moment's consideration will bring clarity into this question.

It will be clear that if we desire to learn in connexion with each individual only whether he remains well, or falls seriously ill, and whether he dies of his illness, or survives, the required statistics can quite well be compiled by perfectly unskilled labour. And it is by such agency that statistics are commonly compiled.

But if we desire to learn what is the number of men

who really fall ill of pneumonia, and the number who really die from it, the clinical skill that will have to be requisitioned will not be less than for an experiential evaluation, such as was suggested above.

Is there any other respect in which the Statistical Method possesses a Theoretical Advantage over the Experiential Method ?

It has, in the course of the preceding analysis of the experiential and statistical methods, been elicited that the statistical method employs, for purposes of numerical notation, a quite arbitrary scale of values ; that it is, in contrast to the experiential method, a method of restricted outlook ; that there are a very large number of cases to which the method cannot be applied ; that it is not capable of bringing to light finer differences ; and that it demands, if the results are not to be of inferior value to those of the experiential method, the application of exactly the same measure of clinical skill.

In all this there is absolutely nothing to justify the superior prestige which attaches to the statistical method. And we are, at the conclusion of our long analysis, left in the position of having to attribute that superior prestige simply to misconception, or of having to look further afield for a respect in which the statistical method has the advantage over the experiential method.

In such a case the indication is always to look further afield, and it here behoves us to extend our search into the sphere of morals. That is perhaps the only sphere which we have left unexplored.

The solution of the problem would indeed seem to lie here. It is impossible to shut our eyes to the fact that the statistical method makes appeal to everyone who is ranged on the side of intellectual morality ; and the man would be blind who failed to see that the propaganda in favour of proceeding everywhere by the statistical method is inspired by the higher morality.

Do Considerations of Intellectual Morality prescribe that the Statistical Method should be everywhere brought into Application ?

We have seen that the statistical method makes its appeal to all who look forward to the rays of the mind penetrating everywhere unhindered. The strength of that appeal lies in the fact that the statistical method is believed to provide effective safeguards against moral shortcomings on the part of the observer and evaluator —shortcomings such as a departure from impartiality ; a holding back of facts which ought to be disclosed ; and a laying claim to unwarranted authority.

The statistical method does, in point of fact, offer against these certain safeguards.

The observer who is blinded by intellectual, personal, or financial bias, but is constitutionally honest—and this is the type of observer against whom we have to be upon our guard—need only employ the statistical method to find himself estopped from overrating the cases which bear out his theories ; and from underrating or putting out of sight cases which have turned out inconveniently for those theories. The experiential method gives opportunities for such departures from morality.

It is not only against the *suppressio veri*, it is also against the *suggestio falsi* that the statistical method safeguards us. If we compel a man to set out his observations in the form of a statistical table he will not, in the case where he has only a restricted experience, adopt the tone of a man who has had a wide experience. We can never feel absolutely sure that this is not being done when a man enunciates an experiential judgment.

In consideration of these facts the statistical method has come to stand for certain moral ideals. It stands for the ideal of clearing one's mind of bias ; for the ideal of making a full disclosure of the facts, and submitting all one's data to the court of appeal of one's fellow-workers ;

and for the ideal of disclaiming all authority except that derived from the observations one has actually put on record.

It will, perhaps, appear as if these considerations had fully vindicated the prestige of the statistical method. But there is something more to be taken into consideration.

(*a*) It is important in connexion with the question of the warping of the observer's judgment by *bias* to realise that this cannot really count as a very formidable obstacle to scientific advance.

Bias, in point of fact, never does acquire sufficient dominion over the mind to influence its decisions when it is adjudicating upon a crucial experiment or upon a series of quasi-crucial experiments. It has displayed its full power when it has succeeded in perverting our judgment where we are dealing with a twin series of substantive and control cases, between which there is a comparatively small average difference. Let it be remembered that in such a case the decision may, even for a dispassionate mind, be a difficult one.

Let us further note that bias, begotten as it is of self-interest, will affect only the verdicts of the original observer and of those who have definitely taken sides for or against him; and the rest of the world will be unprejudiced.

These considerations may, perhaps, have availed to rectify one of the values which weigh in the comparative estimate of the statistical and experiential method.

We may revalue another of those values by considering whether the statistical method does really provide complete security against the intrusion of bias into the observer's judgment.

In point of fact, it falls very far short of doing this. Whenever the statistician has free choice in the matter of the criterion which is to govern his classification—and he very often has such free choice—he can turn this

choice to advantage in the interest of the particular cause which he happens to have at heart.

It is not only the scientific observer's mind which may be warped by bias. Even that of the arm-chair statistician may be warped. Personal bias may influence him in his choice of authorities. His principle of doctrinaire impartiality may convince him that one observer's word is always as good as another's. And the bias of his craft may persuade him that any opinion which is formulated in figures is to be believed against any consensus of opinion which is not so expressed.

The fact that the statistical method is beset by all these forms of bias must go down in the account against it.

When they have all been set down in the account, it will, perhaps, be a question whether the statistical method has, from the point of view of safeguarding us against the intrusion of bias, any advantage over the experiential method.

(*b*) Passing to the next issue, it does, at a first glance, seem as if the statistical method had over the experiential method an absolutely undeniable advantage from the point of view of the *disclosure of the data* upon which the observer's judgment has been formed.

But when we come seriously to make enquiry whether in the case of statistics the cards are really on the table, the answer must inevitably come that the mere setting down of the serial numbers, or, as the case may be, of the names of the patients, is not a fulfilment of the ideal of setting forth the data in such a manner as to make it possible for the reader to control the judgments of the observer. Except for the fact that we learn the number of cases observed—and this information could, of course, be supplied in connexion with an experiential evaluation—we are in no better position to check the accuracy of our observer's data when he uses the statistical, than when he uses the experiential method. We are, for instance, in the case of statistics of pneumonia, compelled to accept

it that every man who is set down as having pneumonia really had pneumonia, and that every man who is set down as having died of pneumonia really died of it. And, of course, we are compelled to accept it that there were not among the cases which came under observation any cases where the diagnosis was doubtful. Statistical observers do not seem to come across such cases.

(*c*) There remains the issue as to whether it is in the interests of science, and accordingly for all of us a rule of the game, to accept the doctrine concerning scientific authority recently set out by Professor Karl Pearson in the dictum,[1] "*The day of authority in any branch of science has gone by. . . . Statistics on the table please.*"

The scientific observer is here told in almost so many words that he must never presume to enunciate an experiential conclusion in any authoritative tone; that he must never, even in the case where he happens to be an expert, claim to be listened to except on the ground that he has been a vehicle through which a certain number of data have been put on record; and that, so long as he employs the experiential method, it is not allowable for him to maintain his opinion against even a quite non-authoritative worker who employs the statistical method.

When we reflect upon this doctrine of socialistic egalitarianism in science, it comes home to us that, while it may be permissible to rank all men as equally competent observers with respect to things that admit of being measured by carpenters' rules, or of being weighed upon grocers' balances; and to rank as the most authoritative on these matters, the man who reports the largest number of observations; this doctrine cannot find application in medicine; for here in many cases truth can be arrived at only by exceptional skill, and a very delicate calculation of probabilities. And in medicine the coefficient of error of our methods is such that no one would choose the

[1] *Biometrika*, July, 1911, "The Opsonic Index—Mathematical Error and Functional Error."

man who records the largest number of cases as the best guide to truth.

The doctrine of Professor Karl Pearson may further be considered in its relation to the quite non-authoritative scientific observer. It means a great deal to the *amour-propre* of such an observer. In the *first* place, it promises him that, if he will but employ the statistical method his evaluations will be of more account than those of any expert who employs the experiential method. *Secondly*, it promises him that if he employs the statistical method he will not, like the man who employs the experiential method, be required to keep always before him the Hippocratic monition : *experientia fallax, judicium difficile.* And, *finally*, the doctrine teaches that, although the expert who employs the experiential method ought not, even when he has behind him a certain consensus of expert opinion, to go so far as to say that he and others have *satisfied themselves* of the truth of a thesis ; the non-authoritative observer, who employs the statistical method, will in every case be entitled to assert—he against any consensus of expert opinion—that he has *proved* his thesis. One often wonders whether the statistician imagines that cumulative experiments have the value of crucial experiments, and that the statistical method of casting up the results can rectify inaccurate observation.

Finally we come to the arm-chair statistician who claims to sit as judge of appeal upon all evaluations of cumulative experiments. As we consider him and realise that he has ruled out all authority in science saving only that of his craft, it comes home to us that the wheel has come full circle, and that the programme of socialistic egalitarianism —the programme of abolishing in every branch of science the despotism of the expert—has ended in the setting up the statistician as dictator wherever in any part of the field of knowledge the method of cumulative experiment comes into application.

When it is made a matter of reproach against the

experiential method that it encourages scientific workers who have served a full apprenticeship to arrogate to themselves unwarranted authority in their special department of observation or experiment; let it be borne in mind that the statistical method encourages the comparatively inexperienced observer to put forward his evaluations as final; and that it invites the man who only collects and digests other men's observations to assume the rôle of a universal arbiter and a final referee.

Looking back now over what has preceded it will be borne in upon the reader, on the one hand, that medical statistics are for the most part nothing more than the data of imperfect clinical methods set out in unwarrantably precise figures; and, on the other hand, that we have in connexion with the statistical method, just as with the experiential method, to reckon with opportunities for the intrusion of bias; with a defective realisation of the ideal of a complete disclosure of the data; and with the assumption of unwarranted authority on the part of the evaluator.

The reader will probably have arrived at the conclusion that there is in all these respects little or nothing to choose between the two methods of evaluation; and he will now desire to pass from the abstract to concrete (or as he would express it from theoretical to practical enquiry) and to ascertain (*a*) how the experiential method approves itself under the test of actual practice, and (*b*) under what conditions an experiential evaluation may be accepted as conclusive, or must, if accepted at all, be accepted with great reserve.

Has the Experiential Method approved itself in actual Practice as a Trustworthy Method, and under what Circumstances may an Experiential Evaluation be unhesitatingly accepted?

Perhaps the best way of conducting this enquiry will be to take examples of medical truths which are acknow-

ledged to be quite unassailable, and to ascertain how these were arrived at and why everyone is logically compelled to accept them.

We may take first the proposition that *sulphur ointment is an infallible remedy for itch*. Consideration shows that we have here a proposition which sets forth the result of an experiment undertaken in ideally simple conditions (the experimental conditions are ideally simple inasmuch as the *causa morbi* is directly acted upon by the therapeutic agent); and which gives, when properly carried out, always the same result. In short, we have alighted upon a proposition which is based, not upon a series of cumulative experiments, but upon a crucial experiment.

None the less the example is not without its lesson for us. When we examine ourselves as to whether we accept such a proposition as this without any reference to authority—that is to say, when we ask ourselves whether the proposition can be accepted as true apart from a guarantee that the crucial experiment was accurately carried out and that its results were accurately observed —it immediately becomes plain that the thesis is not accepted without guarantee. It is accepted upon the authority of trustworthy witnesses known to be competent to carry out the experiment and to control its results.

We thus learn that "the day of authority has" *not* "gone by" and that endorsement by authority is an indispensable requirement, even in connexion with the ideally perfect method of proof: that by the crucial experiment. *A fortiori* it will be a requirement also in connexion with cumulative experiments.

We now pass on to take up the consideration of universally accepted truths which are based upon such experiments. I may here take as examples the thesis that *quinine is an effective therapeutic agent in malaria; that salvarsan is effective in syphilis; and that staphylococcus and streptococcus vaccines are effective in acute*

localised staphylococcic and streptococcic infections. These statements are not built upon data drawn from crucial experiments (for *treated cases* do not all eventuate in a cure or improvement, nor do all *untreated cases* turn out unfavourably) ; they are based upon cumulative experiments (*treated cases* in the large majority of which there is a favourable event, and *untreated cases* in the large majority of which there is an unfavourable event). When we now enquire by what method the data of these experiments were marshalled and evaluated there will, from everyone who is in touch with medical science, inevitably come the answer that the experiential method was here in every case brought into application ; and that the statistical method, where it has in connexion with any of these methods been resorted to, was employed merely to supplement and refine upon the conclusions already arrived at.

So far clearly nothing more has been established than that it is possible to arrive by the experiential method at unassailable conclusions. And it behoves us before putting forward for acceptance any conclusions which have been reached by this method, to define the conditions under which an experiential conclusion will be logically binding upon everybody.

We may solve this problem by asking ourselves in connexion with the therapeutic conclusions which are in question above what it is that leads to their universal and unqualified acceptance.

Two things have contributed to this : (1) The fact that we have on record that *a very large proportion* of the treated cases run a *very much shorter and conspicuously more favourable course* than untreated cases, and (2) the fact that the medical profession, so far as it has experience of these remedies, *unites* in this verdict.

The fact that we have it put on record that the *majority of the treated cases run a very much shorter and conspicuously more favourable course* than the average untreated

case makes it practically certain that the witnesses who report their impression cannot have been misled by their imaginations, or by whatever working error may attach to the method of evaluation ; and that their conclusions must consequently rest upon a genuinely observed difference in the clinical event of the treated cases.

The fact that the medical profession, so far as it has experience of these remedies, is *unanimous* in its favourable verdict is evidence that they are signally effective. For on no other conceivable hypothesis could it happen —it clearly could not happen by chance—that every doctor who has experience of these remedies should have the firm impression that there were in the group of cases —ordinarily a very small handful of cases—which he has himself seen appreciably more treated cases that did well than untreated.

The solution of the problem as to what experiential conclusions are not, and what are, universally binding would accordingly appear to be as follows :—

(*a*) *Experiential judgments with respect to which there is among observers a serious difference of opinion need not be accepted.*

(*b*) *Experiential judgments to which every qualified observer subscribes must be accepted.*

We may deal with these *seriatim.*

(*a*) Where there is a conflict of opinion between observers the proper course to pursue is to appraise the relative weight of the authorities who are ranged over against each other. It will be clear, when we consider that a statistical evaluation by a single observer represents nothing more than the judgments of one individual upon one set of cases, that a disputed issue cannot be set at rest by an individual observer bringing into application the statistical method.

(*b*) The doctrine of the probative value of a consensus, or a practical consensus, of expert opinion, and in particu-

lar the doctrine that the unanimously favourable, or unanimously unfavourable verdict of medical men is conclusive on the question of the efficacy or inefficacy of a method of treatment, will encounter objection in the minds of the unthoughtful.

The train of reasoning which commends itself to these runs somewhat as follows: "Unanimity of expert "opinion does not furnish any real guarantee of truth. "If it did, the Medical Profession would not, time and "again, have accepted unanimously—as it did for instance "in connexion with blood-letting—experiential conclu- "sions which the progress of knowledge has compelled it "to abandon. And now just let me ask," concludes our objector, "is it conceivable that the Medical Profession "would not have been saved from such gross errors if "it had brought into application the statistical method?"

There are in this argument—and it is this argument more than any other which is responsible for the acceptance of the statistician's estimate of the superiority of his method over the experiential—two fallacies:—

(1) The *first* fallacy lies in the institution of a comparison between things that are not *in pari materia*. In other words, the statistician is here comparing conclusions arrived at by the experiential method with conclusions arrived at by the statistical method—without paying any regard to the circumstance that he is considering, in the one case, conclusions deduced from a series of substantive experiments *unsupplemented by controls*, and that he has in view, in the other case, conclusions deduced from substantive experiments *supplemented by controls*.

Now it is clear that, even if we rank statistical evaluation as a notable advance in scientific methods, we cannot by any possibility rank it as of equal importance with the step that was taken when the employment of a series of control experiments—an element in experimentation, which was unheeded in the days of blood-letting—came to be insisted upon. But the statistician takes credit to

himself for every advance in those departments of science which proceed by the method of cumulative experiment, and it is hid from him that the credit is really due to that gradual evolution of a logical conscience in man, which has brought it about that control experiments are now a recognised requirement in connexion with all cumulative experiments.

In point of fact it was not the bringing into application of the statistical method, but the undertaking of control experiments—that is to say, the treatment of patients without bleeding, and the comparison of these by the experiential method with the previous cases treated by bleeding—which led to the general abandonment of blood-letting.

(2) The *second* fallacy lies in making the assumption that a method of evaluation is discredited if it can be shown that an erroneous conclusion has been arrived at by its means. It is clear that if this sufficed to establish the illegitimacy of a method, both the experiential and the statistical methods of evaluation, but *in primis* the latter—upon which the popular verdict is that " statistics will prove anything "—would be irretrievably discredited.

In passing judgment upon any method of evaluation we are entitled to ask that the method shall be judged by its results in the case where the rules have been strictly observed.

It will be clear that the doctrine of the probative value of a consensus of expert opinion is in no way invalidated by such a train of reasoning as that which we have been reviewing.

In reality we are all of us recording machines—recording machines of the most diverse patterns—and when each several machine registers one and the same impression the correctness of such record is established beyond doubt. The general sense of mankind proclaims this in the dictum : *Securus judicat orbis terrarum.* It

again enunciates this principle in the formula : *Quod semper ; quod ubique ; quod ab omnibus.*

And if it stands fast that what is given in the experience of all is true, how shall this not hold also—always with the proviso that untreated as well as treated cases are included in every experience—in our difficult and distracted science of medicine ?

SECTION III

ENQUIRY INTO THE VALUE OF ÆTHYLHYDROCUPREINHYDROCHLORATE IN THE TREATMENT OF PNEUMONIA ; AND DISCUSSION OF THE QUESTION AS TO WHETHER WE OUGHT IN THIS ENQUIRY TO BRING INTO APPLICATION THE METHOD OF EXPERIENTIAL OR THAT OF STATISTICAL EVALUATION

With this we have completed our general analysis of the two methods of evaluation which are available for use in connexion with cumulative experiments ; and we have now to decide which of these to bring into application in investigating the question as to whether the course of pneumonia is favourably influenced by the exhibition of Morgenroth's drug.

We have here an enquiry which is confined to a very few observers each working upon a dissimilar case material, and moreover an enquiry in which the verdict must, for a reason which will immediately appear, be given upon the observation of a very restricted number of cases. These are points which render the statistical method valueless for our purposes and which invite, if indeed they do not dictate, the employment of the method of experiential evaluation.

In this connexion it will be clear (1) that fallacious results will be arrived at if we add together the figures of different observers when these figures refer to groups of

pneumonic patients who are not comparable *inter se* from the point of view of case-mortality; (2) that what we want in a case like the present is, not the aggregate of all the observations, but the separate verdicts of the individual observers; and (3) that where we are confined to the observation of a very limited number of cases the employment of the experiential method is indicated. We ought not in such a case to tie ourselves down to the observation of any one feature, such as the case-mortality, but to give our attention to every significant clinical manifestation.

The reason why, in connexion with the present enquiry, we are not at liberty to experiment upon, and observe sufficient cases to build up trustworthy comparative statistics; and the reason why we ourselves here desisted from bringing into application the statistical method, may be very briefly explained.

It very quickly emerged, as soon as experiments were undertaken upon man, that æthylhydrocupreinhydrochlorate does not come up to the ideal of being at one and the same time poisonous for the pneumococcus, and non-poisonous for the nobler tissues of the patient. The drug is in the human organism—and this holds true also in some measure of its congener: quinine—*optico-neurotropic*.

In the experience of Professor A. Fraenkel,[1] which, as soon as it became available, was cabled to me by Professor Morgenroth, three cases of amblyopia—all of which recovered—occurred among twenty-one pneumonic cases treated with the drug. The dose here appears to have ranged between 1 and 2 grm. daily.

In the meantime, in our experience in Johannesburg two cases,[2] one of which went on to amaurosis, occurred in eight pneumonic patients treated. The doses of

[1] *Berliner klin. Wochenschr.*, 1912, No. 14.

[2] In view of the fact that at this particular juncture two other cases of amblyopia occurred in the W.N.L.A. Hospital in which we were at work apart from the administration of the drug, there is just a possibility that these cases did not occur in relation with it.

æthylhydrocupreinhydrochlorate ranged here between 0·5 and 2 grm. daily. They were administered in some cases by the mouth, in others subcutaneously and in others, again, both by the mouth and subcutaneously.

In a third series of nine pneumonic cases[1] which were treated by Dr. John Parkinson at the London Hospital there were three cases in which the pupils became very widely dilated under the influence of the drug. The doses of æthylhydrocupreinhydrochlorate here ranged between 0·5 grm. or less to 1·5 grm. daily.

It will be appreciated that it was, in view of the two former experiences, out of question to apply the treatment to any large number of patients unless the contingent advantage from the bactericidal action of the drug proved to be such as altogether to outweigh this element of risk.

This is the very kernel of our enquiry. The question we have to decide is not whether there is, or is not, some slight advantage to be obtained from æthylhydrocupreinhydrochlorate. That is an almost academic point ; and a point which could be resolved only if the method of cumulative experiments were capable of giving minutely accurate results. What we have to resolve is the broad question as to whether Morgenroth's drug gives in human pneumonia results such as those which are obtained in the pneumococcic infections of mice ; whether, in fact, we have here a drug which falls into the class of eminently efficacious, or into the class of inefficacious or doubtfully efficacious therapeutic agents. To arrive at a conclusion with respect to this : the really practical issue ; it will suffice to evaluate by the experiential method a very few cases. And the question will be definitely resolved if the evaluations of a series of different observers agree.

Now such consensus of opinion has, in point of fact,

[1] Dr. Parkinson has asked me to put on record here his acknowledgments to the Medical Staff of the London Hospital for their kindness in placing these cases at his disposal.

been arrived at. By the common consent of the two other observers above referred to and of ourselves, and those who saw the cases with us, æthylhydrocuprein-hydrochlorate falls into the class of drugs which are either inefficacious or doubtfully efficacious.

It may be noted that the question as to whether there had not in a small minority of cases accrued a certain amount of advantage to the patient from the exhibition of the drug did, in point of fact, suggest itself in each of the three groups of experiments. But it must be remembered in connexion with such suggestions that they are derived, not from a comparison of treated with untreated patients, but from a comparison of the state of the patient before, with the state of the patient after the exhibition of the drug. And it is clear that this is a method of control which may readily mislead except in the case where we undertake combined *in vivo and in vitro experiments* and establish that the favourable clinical change in the patient has gone hand in hand with an exceptionally conspicuous favourable change in the bacteriotropic power of the patient's blood. Confirmatory evidence of this kind is not available in connexion with any of the three groups of experiments.

It would be ill to bring this enquiry to a close with the conclusion that æthylhydrocupreinhydrochlorate fails to exert a favourable influence on human pneumonia ; and that it fails despite the fact that it is eminently efficacious in the pneumococcic infections of mice, and that it renders, when given in the quantities which here came into application, the human blood-fluids bactericidal. An attempt must be made to account for such failure ; and we must also glance at the question as to whether the toxic properties of æthylhydrocupreinhydrochlorate present an insuperable obstacle to the utilisation of the fundamentally important work of Morgenroth in the treatment of human patients.

In connexion with this latter question, it will suffice

to point out that we have here exactly the same situation as was encountered in connexion with the application of both atoxyl and arsacetin to the treatment of trypanosomiasis and syphilis. It is familiar matter that difficulties such as here confront us were triumphantly overcome by Ehrlich when he gave us in salvarsan an effective and *non-optico-neurotropic* preparation.

Turning to the problem which presents itself in connexion with the inefficacy or practical inefficacy of the drug as a remedial agent in human pneumonia, two possible explanations suggest themselves :—

(1) It is conceivable that the advantage, which one might expect to reap from the circumstance that a bactericidal power is conferred upon the blood-fluids by æthylhydrocupreinhydrochlorate, might be neutralised by some other antibacterial property diminishing, or going lost from the blood. I have often taken occasion to point out that when a minimal quantity of an ordinary antiseptic is added to the blood its phagocytic power is completely abolished. This question was investigated by us in connexion with Morgenroth's drug in the *in vivo and in vitro* experiments reported on pp. 14 and 15 *supra*. The comparative estimations of the opsonic power of the serum before and after the exhibition of the drug, which are there set forth, show that this power is quite unaffected. Furthermore, it was very clearly brought out in an experiment in which graduated additions of æthylhydrocupreinhydrochlorate were made to phagocytic mixtures, that this drug does not exert any sensible toxic effect upon leucocytes until concentrations which are at least twentyfold stronger than would correspond to the medicinal doses which we employed are arrived at.

It must, however, not be definitely concluded that the bactericidal power which the phagocytes are capable of exerting upon bacteria is maintained intact. We discovered in the course of our work that the phagocytosis which occurs in ordinary phagocytic mixtures, in phago-

cytic mixtures made with whipped blood, and also in phagocytic mixtures made with all forms of decalcified blood, leaves all the ingested microbes alive, while the phagocytosis which is obtained when blood direct from the vessels is mixed with the pneumococci kills large numbers of these (up to 600,000 per cubic centimetre of blood). Now, inasmuch as this *phagocyto-bactericidal power*, which must be the useful factor in phagocytosis, is so easily interfered with, it is at any rate conceivable that it may be interfered with by æthylhydrocuprein-hydrochlorate.

Owing to the circumstance that this aspect of the matter was not fully apprehended by us at the time when we were experimenting on man with Morgenroth's drug, we are not in a position to say whether or not the phago-cyto-bactericidal power which the blood exerts upon the pneumococcus is interfered with by the exhibition of the drug.

(2) But, as already suggested above, there is also another possible solution of our problem. That solution is to be sought along the lines which were followed by me thirteen years ago, in seeking an explanation of the fact that infecting micro-organisms maintain themselves alive in the tissues of patients who have made effective immunising response, and who have in their blood a large provision of antibacterial substances. I showed in a paper written in conjunction with Lamb,[1] that the microbes which maintained themselves alive in these cases were to be found, not in the blood-fluids which contained the antibacterial substances, but only in those regions of the body to which the blood-fluids with their bacteriotropic substances had very restricted access. Now, this doctrine of the *non-bacteriotropic nidus* has an application also in the case where the bacteriotropic agent is a drug. It no doubt supplies the explanation of

[1] *Vide* Wright, "Studies on Immunisation." Constable, London. pp. 36–44.

the fact that the *Spirochæta pallida* can maintain itself alive in the body of a patient whose blood has been rendered bactericidal by the injection of salvarsan. And we need only institute a comparison between brawny swelling of the subcutaneous tissues and the condition of the consolidated pneumonic lung to appreciate that the conditions in the two are very similar, and that in each case the influx of bacteriotropic substances from the blood will be prevented by the circumstance that the tissue spaces are filled in with coagulated lymph. We have here clearly a factor which would account for the success of Morgenroth's drug in mice, where the pneumococcic infection takes the form of a septicæmia ; and for its failure in human pneumonia, where the drug would have only restricted access to the infecting microbes.

In bringing this first part of my report to a close, I desire to thank my friend Professor William Bulloch, whose watchful eye misses nothing in scientific literature, for calling my attention to Professor Morgenroth's work. To Professor Morgenroth himself I owe a debt of gratitude for placing his experience unreservedly at my disposal, for keeping me informed with regard to the work which was in progress, and for obtaining for me, by his good offices with Messrs. Zimmer, an ample supply of æthylhydrocupreinhydrochlorate. I owe a similar debt of gratitude to Dr. John Parkinson for his generosity in placing at my disposal full notes of the cases which were treated by him.

PART II

On Prophylactic Inoculation against Pneumococcus Infections, and on the Results which have been achieved by it.

IN the Introduction to Part I, the broad principles which must guide us when confronting bacterial disease were elucidated. It was explained that whether the object we have in view is prophylaxis, or cure—that is, whether, as in prophylactic inoculation, we endeavour to kill off microbes immediately upon their entrance into the body before they have produced disease; or whether, as in medicine practised as a science, we try to kill off bacteria when, by invading the body in large numbers, they have already produced disease—our task is to supply to the organism substances which are specifically *bacteriotropic:* that is, substances which make a chemical attack specifically upon the microbes of disease.

We saw that in connexion with each several disease two paths of research open out before us.

On the one hand there is the path of *pharmaco-therapy.* Following this, we may come to an effective and non-poisonous specifically bacteriotropic drug.

There is on the other hand the path of *immuno-therapy.* Following this, we may come to an effective vaccine—i.e. to a vaccine which will, when administered in proper dose, stimulate the chemical machinery of the patient to elaborate the required specifically bacteriotropic substances.

We have here to deal with the *immuno-therapy* of

pneumococcus infections, and in particular with the employment of vaccines in the prophylaxis and treatment of pneumonia.

It will not be amiss to begin by setting out the evidence which establishes that the pneumococcus is the microbe which is the causal agent of the pneumonia on the Rand.

TABLE I

Data of Blood Cultures and Lung-Puncture Cultures undertaken upon Cases of Pneumonia in Tropical Natives treated in the Hospital of the Witwatersrand Native Labour Association.[1]

Nature of the bacteriological observation.	Number of cases examined.	Number of cases in which the pneumococcus was found.	Number of cases in which the cultures remained sterile.	Number of cases in which a microbe other than the pneumococcus was found.
Blood cultures (1 to 20 c.c. of blood)	390	99*	277†	4‡
Lung-puncture cultures	53	34§	18‖	1‡

* Of these, 56 (i.e. 56 per cent) succumbed. † Of these, 76 (i.e. 27·5 per cent) succumbed. ‡ The micro-organism which grew was in each case one of the coli group. § Of these, 10 succumbed. ‖ Of these, 6 succumbed.

The nature of the bacterial infection which was to be combated having been set at rest, our principal task stood out clearly before us. It was to prepare vaccines of the pneumococcus ; to ascertain, if possible, what was the best form of vaccine ; and above all to determine the effective and, so far as might be possible, the *optimum* dose of the vaccine, and the best method of application.

We may with advantage begin with a brief description of the methods we adopted in preparing the vaccine ;

[1] It may be explained that this Hospital is attached to the depot to which all Tropical Native Labourers arriving at Johannesburg are drafted for subsequent distribution to the mines.

and we may then, before dealing specifically with immunisation against the pneumococcus, call attention to those broad general principles with regard to dosage, and the *modus operandi* of vaccines, which would appear to be deducible from the experience won in connexion with immunisation against other bacterial infections.

SECTION I

PREPARATION OF PNEUMOCOCCUS VACCINES

We experimented somewhat extensively with a view to selecting for use a medium which should give a very copious culture of pneumococcus.

Varying in a methodical manner the peptone, extractives and alkali of ordinary peptone broth, and then making to such media graduated additions of human serum, we found that very copious cultures of pneumococcus were regularly obtained with a medium which contained (*a*) 1 per cent of peptone and 1 per cent of lemco ; (*b*) $2\frac{1}{2}$ to 5 per cent of human serum ; and (*c*) an amount of alkali fixed by neutralising to phenolphthalein, and then adding 6 c.c. of normal acid solution to each litre of medium.

During the first couple of months of our work in Johannesburg we worked with a medium composed as above, but finding that we obtained much more copious cultures by adding up to 1 per cent of glucose to the above-mentioned medium we employed such serum glucose broth in most of our subsequent work. We would, however, point out in this connexion that where such a serum glucose broth is employed it is necessary to be constantly on the watch against the occurrence of autolytic processes which go, it would seem, hand in hand with the development of acid in the culture medium.

For these autolytic processes[1] may, even when they stop short of an actual disintegration of the microbes, deprive the bacteria of their power of staining with aniline dyes, and so give rise to formidable fallacies in standardising the vaccines.

Our vaccines were in all cases made from cultures which had grown for twenty-four to thirty-six hours. They were standardised by enumeration by the method devised by one of us which is now familiar.

The cultures were killed by exposure to a temperature of 55° to 56° C. for half an hour.

An addition of ½ per cent of carbolic acid was then made to the vaccines.

SECTION II

GENERALISATIONS WITH REFERENCE TO THE *MODUS OPERANDI* AND DOSAGE OF VACCINES, AND CONSIDERATIONS SUGGESTED BY EXPERIENCE WON IN CONNEXION WITH PROPHYLACTIC AND THERAPEUTIC INOCULATION GENERALLY

Whenever an *antigen*—and we mean by an " antigen " an alien molecule whose incorporation incites the chemical machinery of the body to immunising response—comes into operation upon the tissues, these react to that attack by producing *antigeni-tropic* and *antigeni-clastic substances*—i.e. substances which combine with, render inert, and break down the antigen.

It is a characteristic feature of such reactions of immunisation that the output of antigeni-tropic and antigeni-clastic substances is in the ordinary case much in excess of what would suffice for the neutralisation and disintegration of the quantum of antigen which calls forth their production.

[1] It may be observed in passing that we found that the culture fluid in which autolysis has occurred did not exert any bactericidal power upon the pneumococcus.

The reaction which is evoked by the inoculation of a bacterial vaccine is merely a special case of immunising response. By it bacteriotropic substances, and among these, substances which break down the bacterial protoplasm—*bacterio-clastic* substances—are produced. And in the ordinary case the inoculated organism is, at the end, left in possession of an increased store of these protective substances. We take advantage of this in prophylactic and therapeutic inoculation.

Passing from the consideration of the *modus operandi* of bacterial vaccines to their dosage it is essential to realise *in limine* that we must be on our guard against importing into the study of this question preconceptions derived from experience with drugs.

When for instance we come upon the fact that there are reported, in connexion with therapeutic inoculation, good results from the administration of minimal doses of vaccines, and also equally good results from the administration of doses 1000 to 100,000 times larger, it would be quite wrong to assert upon the basis of an experience with drugs that these divergent reports are contradictory and irreconcilable.

To rush to such a conclusion would be to close one's eyes to the fact that provision is made in the organism for combating, on the one hand, trivial localised infections and, on the other hand, severe septicæmic infections—in other words, for making immunising response both to small, and to relatively large, doses of bacterial antigens.

Again it would be fatal to conclude from an experience of drugs that, if a particular dose of vaccine produced serious symptoms, a tenfold larger dose would of necessity produce graver symptoms, and still larger doses a rapidly fatal result.

That would be to leave out of reckoning the fact that there are in the organism compensating arrangements ; and that there is provision for ignoring, or at least for provisionally ignoring and postponing the attack upon,

massive bacterial infections which are upon too large a scale to be disposed of immediately.

In connexion with the dosage of bacterial vaccines we have to guide ourselves by a series of general principles, which have either emerged in the course of the general study of immunisation, or have been derived from the direct measurements of the bacteriotropic power of the blood made in connexion with the inoculation of bacterial vaccines.

Of these general inferences, the following are perhaps for us the most important :—

In the case where a bacterial vaccine is incorporated in minute quantity directly into the subcutaneous tissue one would on *a priori* grounds anticipate that the whole of it would be " anchored " at the seat of inoculation, with the result that the immunising response would be confined to this region and its lymph channels ; and with the further fundamentally important practical result that the effect produced upon the general system by the inoculation would not differ from that which would be produced by a conveyance of a small quantum of protective substances into the blood.

The inference that the *minimal effective dose* of vaccine calls forth only a *local immunising response* is confirmed by the fact that, so far as we know, the only change in the blood after the injection of such a dose is a rise in its bacteriotropic power.

When a larger dose of bacterial vaccine is inoculated into the subcutaneous tissue—i.e. when the dose of bacterial antigen exceeds that quantum which can be anchored at the seat of inoculation—one would expect, first, an influx of vaccine, or of its derivative antigen, into the blood-stream ; and after this, in the ordinary case, as soon as the antigen has come into operation upon the general tissues, a *systemic immunising response*, with an inflow of protective substances into the blood.

We have confirmation of this anticipation in the fact

that we obtain after the inoculation of a moderate dose of vaccine, first, a *negative*, and afterwards a *positive phase* of bacteriotropic power—in other words, *first*, a phenomenon of de-immunisation, and then a phenomenon of immunisation.

But clearly the achievement of a systemic immunising response would be conditional upon the antigen remaining free in the blood ; and upon the concentration of the antigen being, after dilution with the whole volume of blood, such as to permit of its coming into effective operation upon the tissues.

There are here two possibilities. There is, on the one hand, the possibility that the antigen might be too concentrated at the seat of inoculation to produce a local immunising response ; and that it might, after dilution with the whole volume of the blood, and eventual neutralisation there, be reduced to the point of ineffectiveness. We should in such a case have neither a negative nor a positive phase. There is, on the other hand, the possibility that the antigen might, even after it had been diluted with the whole volume of the blood, still be too concentrated to be effective. We should in this case expect a negative phase which would not be followed up by a positive phase.

Only methodical experimentation could show exactly up to what point these theoretical possibilities are realised. It is, however, practically certain that an overpowering dose of vaccine—typhoid vaccine is the vaccine we have here in view—produces a well-marked and enduring negative phase.

We have not yet come to the end of the complications which have to be unravelled. We have to account also for the facts :—(*a*) that a dose which in one man produces no constitutional commotion will in another produce severe disturbance ; (*b*) that after a certain dose of vaccine has been arrived at, further increments produce no further increase in the constitutional disturbance,

and no further reduction in the bacteriotropic power of the blood; (*c*) that the infected organism is generally much more sensitive than the uninfected organism, both to the toxic effect of the homologous vaccine, and also to its de-immunising and immunising effect; (*d*) that the organism when wasted by severe and long-lasting infection becomes again more tolerant of the vaccine; and (*e*) that a similar tolerance is established in a patient whose blood has been tampered with by the incorporation of large doses of vaccine.

In connexion with this series of facts we shall do well to reflect that before a vaccine can take effect upon the tissues and before an immunising response can be evoked from these, the bacterial protoplasm would have to be brought into solution by the blood-fluids. Further, the bacterial extract which bacteriolysis would then have furnished might, perhaps, have to be decomposed in such a way as to set free the antigen.

Three different operative factors might here influence the result :—

(*a*) Each different species of microbe might offer a different resistance to bacteriolysis; and each resulting bacterial extract a different resistance to bacterioclasis.

(*b*) The mode in which the vaccine is incorporated might tell upon the result. In the case where it is incorporated into, and remains lodged in, the subcutaneous tissue one might, inasmuch as here only a small quantum of lymph comes into operation upon the vaccine, expect to obtain, at best, tardy and incomplete bacteriolysis and bacterioclasis. Where the vaccine is carried on into the circulation, or is incorporated directly into the blood-stream, one might expect a more rapid and complete setting free of the antigen.

(*c*) Natural differences in the bacteriolytic and bacterioclastic powers of the blood of different individuals, and also differences referable to foregoing immunisations or de-immunisations, might come into play.

All these different considerations suggest to the mind that we have to consider in inoculating, not the actual quantum of vaccine we incorporate, but the quantum of antigen which will be set free from it in the organism of the patient.

This hypothesis would fit the fact that there always comes, in the case where progressively larger doses of vaccines are administered, a point where an increase in the dose ceases to call forth a greater response.

Our hypothesis would explain also the difference in the behaviour of different vaccines. We have in view here the fact that we obtain with a vaccine like typhoid vaccine, which is readily dissolved and presumably broken up by the blood-fluids, a local inflammation at the seat of inoculation ; and, when a sufficiently large dose is inoculated, also constitutional disturbance with a negative phase ; while we obtain neither local inflammatory reaction nor negative phase disturbance, when we are dealing with a vaccine which the patient's blood is incompetent to dissolve and decompose.

Our hypothesis would explain also the fact that a patient who has, as a result of immunisation or auto-immunisation, acquired a greater bacteriolytic and bacterioclastic power, evinces an increased sensibility to the vaccine. For this is what might reasonably be expected to occur if more antigen was set free, and a corresponding quantum of antidotal substances was not available to neutralise it.

And, in point of fact, this would appear to be the condition encountered in the ordinary tuberculous patient. We have here in the blood an increased bacterioclastic power,[1] and in association with this a great sensitiveness

[1] We have found—and this is in consonance with the results of experiments carried out by F. Meyer and Schmitz (*Deutsche med. Wochenschrift.*, 1912, No. 42, p. 1963) on rabbits—that tuberculin, which has been digested *in vitro* at 37° C. with the serum of a patient, gives a marked Pirquet reaction on the skin of a healthy individual who is insensitive to a control insertion carried out simultaneously on another portion of his skin with the same concentration of untreated tuberculin.

to the epidermal application of tuberculin (Pirquet's phenomenon); a greater constitutional sensibility to an incorporation of tuberculin; and a greater susceptibility to its immunising and de-immunising action.

Having once recognised that increased sensitiveness to a bacterial vaccine may be an expression of progress —of course only very lop-sided progress—in immunisation, the way is open to the recognition of the possibility that the condition of tolerance which characterises the patient who is wasted with a long infection, or has been treated with large doses of vaccine, may mean a reduction in the bacterioclastic power of the blood, and so a retrogression in immunity. The failure to react to tuberculin, and the absence of the Pirquet reaction in old-standing and desperate cases of tuberculosis, would perhaps be explicable in this manner.

In conclusion it may be pointed out that, while some of the increased sensibility of the infected to their homologous vaccine may be put down to the account of increased bacterioclastic power, we must recognise that the constitutional disturbance which supervenes in the infected is due primarily to the fact that inoculation produces in them always a secondary auto-inoculation.

We can account for the occurrence of such a secondary auto-inoculation when we consider that there must inevitably follow upon any rise in the bacterioclastic power of the blood a breaking down of microbes and a setting free of antigen in the focus of infection which would correspond to a supplementary inoculation.

It will accordingly be necessary when reckoning the dose for an infected patient to calculate for the dose which we administer being reinforced by the quantum of antigen which will be liberated in the focus of infection.

In bringing this section to a close it may be pointed out that the general principles we have here been considering must be kept in view not only by the practical

worker, but also by the statistician who analyses the results of inoculation.

Certain other general considerations in connexion with the dosage and *modus operandi* of vaccines will suggest themselves as we develop our theme.

SECTION III

ACCOUNT OF THE LABORATORY WORK UNDERTAKEN WITH A VIEW TO FINDING THE OPTIMUM DOSE OF PNEUMOCOCCIC VACCINE AND THE BEST SCHEME OF ADMINISTRATION

When we set ourselves the task of finding out what is the optimum dose of a vaccine and the best scheme of administration we can employ one or other of two different methods.

We can either—selecting as best we can (which means by a more or less haphazard procedure) a "reasonable" dose and scheme of administration—directly undertake a mass-experiment, with the idea of afterwards modifying our dose and programme of inoculation in the light of the statistical results which will come in.

Or, we can in connexion with each small group of inoculations, test the effects we are producing upon the blood with a view to finding out in this way what dose of vaccine and what scheme of inoculation furnishes the best curve of immunisation.

It will be obvious that if we can adopt this latter procedure, and are not quite unsuccessful in our investigations, the possibilities of failure will be reduced, and the prospect of achieving the optimum results will be more favourable.

Influenced by this consideration, our plan of action was made up, and we addressed ourselves immediately to a preliminary study of the blood in its relation to the pneumococcus, in order to prepare ourselves to measure

the rise and fall in protective substances elaborated in response to each different dose of pneumococcus vaccine, and each different method of administration.

With these thoughts and designs we investigated in succession : (*a*) *the agglutinating power of the serum ;* (*b*) *the bactericidal power of the serum ;* and (*c*) *the opsonic power of the serum.* Further—breaking here new ground —we investigated the *phagocyto-bactericidal power* of the unaltered, artificially altered, and reconstituted blood.

AGGLUTINATING POWER OF THE SERUM

We may summarise the result of a number of examinations made directly *ad hoc*, and of a much larger number made incidentally in connexion with measurements of the opsonic power of the blood, by saying that the agglutination reaction is with the pneumococcus only very irregularly obtained. Working with subcultures from the blood- and lung-puncture cultures which were in question above, we found that the vast majority of these gave no agglutination reaction with the blood of any patient. Moreover, in the case of those exceptional cultures which gave agglutination, we obtained the reaction not only with a large number of sera from pneumonic patients, but also with a number of normal sera. By consequence we put aside the agglutination test as one that could not be utilised for the purpose of estimating the effect produced by pneumococcus vaccines.

BACTERICIDAL POWER OF THE SERUM

Previous experiments having taught us that the normal human serum, when mixed volume for volume with progressive dilutions of the bacterial suspension exerts no bactericidal effect upon the pneumococcus ; we elaborated, for the purposes of the present research, a technique which allows of the serum being brought into application upon the pneumococci in a practically undiluted condition.

The technique which realises this requirement may here be briefly described.

The apparatus consisted of looped pipettes, such as are described and figured by one of us in his text-book of technique.[1] A 5 c.mm. volume was marked off upon the stem of each pipette by introducing, by the aid of an automatic pipette, 5 c.mm. of mercury into its distal end ; and then inscribing a pencil mark opposite the upper level of the mercury.

The procedure is then as follows : After re-sterilising the stem and fitting a teat to the pipette, there is aspirated into the barrel a sufficient quantity of 1 per cent serum broth to half fill it. There is then aspirated into the capillary stem—which is, when the broth has passed up into the barrel, left empty—5 c.mm. of the serum to be tested. This done, a bubble of air is drawn into the mouth of the pipette, this is then dipped into a suspension of the pneumococcus placed ready to hand in a tubule, and 5 c.mm. of this suspension is taken into the capillary stem. This done, the distal end of the pipette is brought up against the inner wall of an empty sterile tubule placed upright in plasticine ; and now the 5 c.mm. of the pneumococcus suspension is, by carefully regulated pressure upon the teat, expelled ; while the serum, which follows after, is carried forward to the very orifice so that it may incorporate into itself all the microbes which the suspension leaves behind on the wall of the tube. This accomplished, the serum is, by relaxing the pressure on the teat, carried back into the middle third of the stem of the pipette so as to allow of our sterilising the distal end and sealing it up in the flame.

By this technique we can, if we are employing a series of graduated dilutions of a bacterial suspension, incorporate into our 5 c.mm. volumes of serum graduated numbers of microbes.

[1] Wright, "Technique of the Teat and the Capillary Glass Tube." Constable : London. 1912.

Two further points in connexion with the technique remain to be explained :—

(1) After the serum has operated upon the microbes which have been incorporated into it for such period as we may have decided upon (in our experiments the serum was generally allowed to operate upon the microbes for four to five hours) we fit a teat to the tube ; break off the tip of the capillary stem ; draw up the serum into the nutrient fluid in the barrel of the pipette ; and then incubate for twenty-four hours to ascertain whether the microbes have, or have not, been killed by contact with the serum.

In order to make all go off smoothly in opening up the pipette, we employ one or other of the following devices : (*a*) we draw out the end of the capillary stem into a hair-fine tube before imposing the collapsed teat ; or (*b*) we employ a perforated teat ; or (*c*) we mark the position of our column of serum by inscribing a pencil mark on the stem of the pipette ; then impose a partially collapsed teat ; and then, before breaking off the tip of the capillary stem, regulate by pressure on the teat the air-pressure in the pipette in such a manner as to bring our column of fluid back accurately to the level of the pencil mark.

(2) To find out the number of microbes which we are dealing with in our bactericidal estimation we take another series of similarly graduated pipettes, using enough of these to have two or more for each of the more diluted bacterial suspensions. We fill in these pipettes with the same nutrient fluids, and then—varying the technique from that described above only in the respect that we omit the volume of serum—we draw into separate tubes 5 c.mm. of each successive bacterial suspension ; expel this, driving forward the nutrient fluid to the mouth of the tube, so as to incorporate into it all the microbes which remain behind on the walls ; and then place the series of pipettes in the incubator.

With this method we tested in all 264 samples of serum ; 41 of these were derived from ourselves, 20 were derived from natives in different stages of pneumonia, 27 were derived from uninoculated Tropical Natives, and 176 were derived from Tropical Natives who had been inoculated once or oftener with different doses of pneumococcus vaccine. In the case of the sera derived from the last two classes of persons, we employed in each experiment the pooled serum of a group of two to five patients, counting this, of course, only as one serum. In the case of the sera derived from pneumonic Native patients or from ourselves (who served in each case as controls) each serum was taken in hand separately. The results of the bactericidal estimations thus undertaken may be tabulated as follows :—

TABLE II

Variety of serum.	Total number of observations.	Number of observations in which no microbes were killed by 5 c.mm. of serum.	Number of observations in which 1 to 3 microbes were killed by 5 c.mm. of serum.	Number of observations in which 3 to 9 microbes were killed by 5 c.mm. of serum.	Number of observations in which over 9 microbes were killed by 5 c.mm. of serum.
Normal European	41	36	4	1	0
Native pneumonic patients	20	11	9	0	0
Normal Tropical Natives	27	19	8	0	0
Inoculated Tropical Natives	176	161	15	0	0

We may obviously conclude from these observations : (*a*) that the normal serum of Whites and Tropical Natives does not exert any appreciable bactericidal effect upon the pneumococcus ; and (*b*) that the serum of the Natives does not acquire any appreciable bactericidal power under the influence of either natural infection or inoculation.

At the same time we would point out that, while there is no bactericidal power in the serum which is worth while taking into account in connexion with the study

of the effects of inoculation and auto-inoculation, closer study reveals that the sera which have a high opsonic power, and which manifest from time to time such slight bactericidal effects as are shown in the table above, may perhaps possess an appreciable power of inhibiting the growth of the pneumococcus.

It may, for instance, be noted that the serum of A. E. W., which in seventeen bactericidal experiments gave on three occasions evidence of a slight bactericidal power (5 c.mm. of the serum once killing up to 9 pneumococci), was found when admixed with broth (in proportions of 40 and higher percentages of serum to 60 and lower percentages of broth) to inhibit or retard the growth of the pneumococcus, while the blood of L. C., which gave in ten bactericidal experiments completely negative results, failed to exhibit any growth-inhibiting power. Similar indications were obtained also with the blood of another laboratory worker (A. R. F.).

OPSONIC POWER OF THE SERUM

We had anticipated that the measurement of the opsonic power of the serum would have furnished us with a valuable method for making an evaluation—of course only a partial evaluation—of the protective substances produced in response to the inoculation of vaccines or auto-inoculation. We obtained, however, from much assiduous work devoted to the measurement of the pneumo-opsonic power of the blood of the inoculated and uninoculated natives, and native pneumonic patients, a quite lamentably small harvest of suggestive and interesting facts. It will be worth while, even if only for the sake of the facts discovered by the way, to set out the difficulties which we encountered and the procedures which we resorted to to circumvent those difficulties.

Difficulties which present themselves in Connexion with the Measurement of the Pneumo-opsonic Power of the Serum.

(*a*) The *first* difficulty which presents itself is one to which Rosenow has called attention in the first of the very valuable series of memoirs which he has published on the pneumococcus. The difficulty in question lies in the fact that cultures of pneumococcus freshly isolated from pneumonic cases often fail to give any phagocytosis. After having been for some time baffled with this difficulty, one of us (W. P. M.) found a method of circumventing it, which very often does away with the necessity of making a series of subcultures. This expedient consists in making the suspension of the culture in distilled water instead of in physiological salt solution or nutrient broth. The longer, within limits, the culture is left in contact with the water the greater is the phagocytic count. The favouring influence of treatment with distilled water manifests itself also in the case of pneumococci which have by subculturing become susceptible to phagocytosis. This is shown in the Tables III and V (*infra*).

TABLE III

Serial number of the patient who furnished the serum.	Phagocytic count obtained with pneumococcus No. 92 in watery suspension.	Phagocytic count obtained with pneumococcus No. 92 in 0·85 per cent NaCl suspension.
67053	1·32	0·96
89559	1·60	0·58
69416	6·00	4·5
69419	3·14	1·80
69475	1·08	0·27
69352	6·00	4·80

(*b*) A *second* difficulty presents itself in the fact that phagocytosis is restrained by an excess of microbes in the suspension employed in the phagocytic mixture. To give examples: The pooled blood of five laboratory workers was tested in phagocytic mixture with suspensions of the pneumococcus containing respectively 1800, 900,

300 and 100 millions of microbes. The phagocytic counts obtained with these four suspensions were respectively 1·01, 4·96, 3·16 and 2·28 per cell. In another experiment in which W. P. M.'s serum was put up with an uncounted suspension of pneumococcus and with 2-, 4-, 8-, 16- and 32-fold dilutions of that suspension, the phagocytic counts of the series of dilutions corresponded to 1 ; 3·1 ; 2·65 ; 1·65 ; 1·6 ; and 1·3 respectively.

(*c*) A third difficulty presents itself in the fact that every strain of pneumococcus—and from this point of view every case of pneumonia furnishes a separate strain —gives a different amount of phagocytosis ; and that the order of merit of a series of sera as determined by reference to one strain is not the same as the order of merit as determined by reference to another strain. Evidence of this is furnished by the typical experiments set out in Tables IV and V.

TABLE IV

	Initials or serial numbers.	Phagocytic count with pneumococcus strain 135.	Phagocytic count with pneumococcus strain 165.
Laboratory workers	A. E. W.	1·22	3·20
	W. P. M.	0·78	2·35
	F. C. L.	0·98	1·12
	O. S.	0·78	1·8
Native pneumonic patients	60134	1·18	0·40
	106654	1·17	2·0
	89807	1·33	1·16
	69875	0·78	1·76

TABLE V

	Initials or serial numbers.	Phagocytic count with pneumococcus strain 165 suspended in water.	Phagocytic count with pneumococcus strain 181 suspended in water.	Phagocytic count with pneumococcus strain 181 suspended in 0·85 NaCl.
Laboratory workers	A. E. W.	5·72	2·10	1·35
	W. P. M.	5·61	2·05	1·10
	F. C. L.	3·28	0·10	0·17
	L. C.	3·66	0·85	0·65
Native pneumonic patients	60463	6·10	3·10	2·57
	60556	2·88	0·42	0·27
	60586	2·80	0·07	0·0
	60676	1·18	0·0	0·10

A *fourth* directly presents itself in the fact that different subcultures of one and the same pneumococcus give, even when the suspensions employed contain exactly the same numbers of microbes, quite different amounts of phagocytosis. Differences in the composition of the culture medium here exercise a determining influence. When using cultures grown on agar made up with heated serum we obtained with all sera relatively high phagocytic counts. Cultures grown on agar made up with unheated blood gave on the other hand with ordinary sera a low phagocytic count, and with sera which possessed subnormal opsonic powers no phagocytosis. In other words, we had in the one case a comparatively speaking non-differential phagocytosis, such as is shown in Table IV, first column of figures, and Table V, first column of figures, and in the other case a highly differential phagocytosis, such as is shown in Table IV, second column of figures, and in Table V, second and third columns of figures. But irregularities of this kind were also obtained apart from obvious differences in the culture medium. They were continually manifesting themselves even in the case where tubes from one and the same batch of nutrient medium were employed. This was the most formidable of all our difficulties. It rendered nugatory all our efforts to obtain a series of opsonic readings which should be comparable from one day to another ; and in point of fact it marred and put out of account every one of the immunisation curves which we set ourselves to construct with intent to select for our prophylactic inoculations that dose of vaccine and scheme of administration which should give the maximum immunisation reaction.

One might have supposed that the expedient of employing a control of normal sera—the expedient which has resolved the problem of measuring the opsonic power of the blood to a large variety of microbes—would have provided a way of escape out of these difficulties.

As a matter of fact it fails to do so.

Quite definite conditions must be fulfilled before opsonic measurements which are carried out from day to day in separate operations can be combined into an immunisation curve.

(*a*) We can register *the occurrence of a positive or negative phase* upon condition that we have in our series of measurements a trustworthy base line which runs along at a level well below that which the opsonic power of the patient attains in the positive phase of an appreciable immunising response, and well above the level to which his opsonic power sinks away in the negative phase.

This condition will be fulfilled if we employ for our controls uninfected and uninoculated persons who, except in the fact that they are uninfected and uninoculated, correspond with those we are operating upon ; and further if we take as our fiducial point in each successive examination the arithmetical means of the phagocytic counts of several different control sera.

(*b*) We can register the *dimensions and duration of a negative or of a positive phase* upon condition that we have for our successive measurements, on the one hand, a level base line ; and, on the other hand, a numerical scale, whose divisions remain constant.

These conditions are fulfilled if we employ from day to day a series of control bloods in association with *homologous bacterial suspensions*—meaning here by ' homologous suspensions ' : such as would give with one and the same serum the same amount of phagocytosis.

But where we employ bacterial suspensions which are not homologous and where our control sera differ in opsonic power—and let us here incidentally note that we may expect to find differences in opsonic power in connexion with every microbe which, like the pneumococcus, is a constant or frequent denizen on our mucous membranes—our fiducial point and the value of the divisions of our scale will differ from one day to another.

Now these are, as the reader will have gathered, the conditions with which we have to deal when we set ourselves to measure the opsonic power of the blood with respect to the pneumococcus.

The conditions may be compared with those which would present themselves in a competitive examination in which each candidate had to be separately examined; each being pitted in his turn against a group of control examinees whose average achievements were to furnish the standard of comparison.

It will, on calling up clearly before the mind what would happen under these conditions, be realised that the marks of the competing candidates could not under such a system give an equitable standard of comparison if at one time a stiff, and at another time an easy, examination was set. For in an easy examination each examinee would score more or less the same number of marks, with the result that the controls would be much on a level, and the competing candidate somewhere near that level. This would amount to differentiating in favour of the weak, and against the strong, candidate. For both would in an easy examination be brought inequitably near to the mean. On the other hand, in a difficult examination there would be maximal differences between the marks of the examinees, and the competing candidate who diverged from the arithmetical mean would accordingly be allotted either an unduly high, or an unduly low mark. And this of course would be equivalent to differentiating against the very weak and in favour of the strong candidate. For both would in a difficult examination be spaced out unduly from the mean.

It having by this been made plain that opsonic data which should fulfil the condition of being from day to day comparable among themselves, and quantitatively trustworthy, were out of our reach; there remained for us—and there here remains for the reader—the question as to whether at least qualitative results in the form of a

notification of a rise or fall in the pneumo-opsonic power of the blood could be obtained for our guidance in our practical work.

We have seen above that such information can be secured only when we are employing controls which are uninfected, and which are, except with respect to infection and inoculation, comparable with the patients.

In order to make so far as possible sure of fulfilling this condition, we took as control bloods every day, *first*, our own bloods and those of our fellow laboratory workers (in all four to six European bloods), and, *secondly*, one, two or sometimes three groups of uninoculated Tropical Natives (usually five to ten, and occasionally more Native bloods). We took, it may be remarked, our Native controls from the same gang and race as the inoculated, and we employed every day for our controls the same individuals.

With regard to the Native controls. When we took, as we usually did, two groups of these controls from different tribes, we frequently found that while duplicate specimens of each set of bloods gave concordant results, the two sets not infrequently showed a very wide divergence. We provisionally imputed this to tribal differences. But we afterwards satisfied ourselves that practically every group of uninoculated native bloods obtained from the Witwatersrand Native Labour Association Compound, where we were at work, showed when measured against the European controls quite definite fluctuations in opsonic power, which could not be attributed to a variation in the bacterial suspensions used on different days. And there is in point of fact little doubt that the difficulties which we were labouring with were due to the circumstance that our controls were taken from a population which was furnishing a formidable number of cases of pneumonia, in addition to almost innumerable unregistered cases of mild pyrexia which were probably in large part pneumococcic infections. And when we

proceeded to make daily measurements of the temperature of each control we found that, no matter what precautions had been taken in selecting at the outset, there were always a good number who showed in the course of the ten days or fortnight during which we were taking daily specimens of their blood, slight temperature disturbances—to say nothing of the fact that some of them actually contracted pneumonia.

Coming to ourselves, who were the European controls, we were unsatisfactory in the respect that our normal diversity in opsonic power may quite well have been exaggerated by the fact that some of us (especially A. E. W. and W. P. M.) were, and others of us were not, in daily contact with pneumonia patients. And we were unsatisfactory as controls also in the respect that the arithmetical mean of our phagocytic counts was so much greater than the arithmetical mean of the phagocytic counts of the uninoculated natives that it was quite impracticable to use that arithmetical mean as a standard for a negative phase, or even for a moderate positive phase occurring in a native. We became useful as controls only when it came to registering a maximal immunising response.

This brings us to the summing up of the results of the thousands of opsonic estimations undertaken by us in the course of this research.

Those results—so far as concerns help obtained in the selection of the dose for prophylactic inoculation—may be summed up in the statement that on taking a general survey of the data obtained by our daily comparisons between groups of inoculated and uninoculated natives, and natives suffering from pneumonia, and ourselves, we were able to satisfy ourselves that the doses of 200 to 300 millions which we were tentatively administering at the outset of our work elicit in the native an opsonic response which brings him in the ordinary case up above the level of the uninoculated native, and in the favourable cases

up to the level of the native who is making good immunising response against pneumonia.[1]

In other words, the opsonic response which is in favourable cases elicited in a native by a dose of 200 to 300 millions of pneumococci would seem to be not much below his maximal opsonic response—assuming this to correspond to the best opsonic response met with in the native pneumonic patient.

On the other hand, we must not leave out of view that our opsonic measurements failed to tell us (*a*) what is the optimum dose of pneumococcic vaccine for general use in prophylaxis ; (*b*) what is the best dose to employ in treatment of pneumonia ; (*c*) whether one inoculation ought to be followed up by another, and if so, how soon it ought to be followed up ; and (*d*) whether a single hypodermic inoculation, or (*e*) the same aggregate dose of vaccine distributed in multiple hypodermic inoculations, or (*f*) intravenous inoculations—for we endeavoured to investigate all these points—give the best immunising response.

Excursus No. I.—On the Effect of pooling Sera, and Description of a New Method for testing Sera in Groups.

The method of combining the sera of patients so as to obtain in one operation the average bacteriotropic power of the group is, as will be recognised, almost indispensable to the working out of the optimum prophylactic dose of a vaccine.

The method of pooling which was introduced by one of us for this purpose has in the hands of Leishman served to fix the prophylactic dose of typhoid vaccine.

We ourselves for a long time pooled the control bloods employed in tuberculo-opsonic estimations ; obtaining here results which, as we were dealing with bloods which had appreciably the same opsonic indices, naturally corresponded to the arithmetical mean of the opsonic indices of the component bloods. When afterwards we laid the method aside,

[1] That this level is sometimes higher than that of the uninoculated European will be seen on referring to Tables IV and V and noting that there were among eight pneumonic patients two who had a higher phagocytic count than any of ourselves.

this was done only with a view to securing the valuable cross-check which is, in the case where all normal bloods possess essentially the same opsonic power, obtained by the reciprocal control of one blood by another.

In connexion with the task of fixing the prophylactic dose of pneumococcus vaccine, inasmuch as here not only the inoculated but also the control group is composed of individuals differing widely in opsonic power, we expected to derive quite conspicuous advantage from the procedure of pooling.

This expectation was not realised. While we obtained, with *normal European bloods*, in the exceptional case where their pneumo-opsonic indices agreed very closely, a value for the pooled serum which corresponded very closely with the arithmetical mean of the separate sera ; we obtained, in the case where the opsonic powers of the bloods differed, phagocytic counts for the pooled sera which corresponded in practically every case with that of the constituent serum which gave the highest count.

Quite typical findings are set out in the subjoined table :—

TABLE VI

Indication of the source of the serum.	Phagocytic counts of the separate sera.	Phagocytic count of the pooled serum.	Arithmetical mean of the phagocytic counts of the separate sera.
A. E. W. ..	4·86		
W. P. M. ..	4·0	.. 4·2 ..	4·5
F. C. L. ..	4·6		
A. E. W. ..	4·08	.. 4·4 ..	3·45
F. C. L. ..	2·86		
A. E. W. ..	4·5	.. 4·6 ..	3·1
F. C. L. ..	1·68		
A. E. W. ..	5·4		
W. P. M. ..	2·3	.. 5·1 ..	4·0
F. C. L. ..	4·35		
A. E. W. ..	6·3		
W. P. M. ..	0·48*	.. 6·24 ..	2·8
F. C. L. ..	1·71		

* This was an accidentally hæmolysed specimen of blood.

We may point out, in connexion with these results, that the concordance of the phagocytic count of the pooled serum with the phagocytic count of the most active of the constituent sera is in consonancy with the observation that the opsonic power of a serum is not reduced until a much higher dilution

is arrived at than that reached when, as in these and the subjoined experiments, a serum is mixed with equal volumes of a few other sera.

Very different to the above were the results obtained when we worked with the bloods of inoculated natives, of natives who were suffering from pneumonia, and oftentimes of uninoculated natives who were living exposed to infection in the W.N.L.A. Compound. Here we obtained for the pooled sera values which were, more often than not, much lower than the arithmetical mean of the component sera. A series of quite typical examples are subjoined in Table VII :—

TABLE VII

Indication of the source of the serum.	Phagocytic counts of the separate sera.	Phagocytic count of the pooled serum.	Arithmetical mean of the phagocytic counts of the separate sera.
Inoculated native No. 1	0·38		
„ „ „ 2	1·06		
„ „ „ 3	0·96	0·4	0·91
„ „ „ 4	1·14		
„ „ „ 5	1·3		
Native pneumonic patient	1·75	0·8	1·35
Uninoculated native	0·95		
Native pneumonic patient	0·48	0·4	0·71
Uninoculated native	0·95		
Uninoculated native	0·9	0·72	1·05
„ „	1·25		
Uninoculated native	2·1	0·9	1·67
„ „	1·25		

We are unable to furnish any satisfactory explanation of these findings. It occurred to us as a possibility that the phenomena here in question might be associated with a negative phase, or at any rate with the presence of a pneumococcic antigen in the blood ; but despite the fact that we devoted much labour to the study of the question, we were unable to satisfy ourselves on the point.

Of far greater moment and far more urgent was for us the task of replacing the method of pooling the sera which had been recognised as fallacious by some better method.

After a time we succeeded in finding such a method. It is a procedure for the pooling of a series of phagocytic mixtures.

The essential features are as follows : We take our group of bloods, a group of usually four to six bloods. Using then for each blood a separate capillary pipette we make our series of phagocytic mixtures ; and working as rapidly as possible

we range these side by side in separate drops on a glass slide. We then take in hand a somewhat larger and more roomy capillary pipette ; inscribe a fiducial mark on its stem ; and then aspirate into this an equal volume of each phagocytic mixture—dividing off the mixtures in each case by a bubble of air, a minute volume of physiological salt solution (taken up from a watch-glass placed ready to hand), and another bubble of air. This done we seal up the tip of the pipette, and insert it into the opsonic incubator. After incubation the phagocytic mixtures are blown out on to a slide so as to form a common drop (the intervening drops of salt solution may if desired be discarded). Finally, after the contents of the drop have been repeatedly drawn up into, and blown out from the pipette, so as to effect thorough intermixture, we make our films.

Table VIII

Indication of the source of the serum.	Phagocyte counts separately.	Arithmetical mean of the phagocytic counts of the separate sera.	Phagocytic counts of phagocytic mixtures pooled before incubation.	Phagocytic counts of phagocytic mixtures pooled after incubation.
Uninoculated native No. 1	1·9			
„ „ „ 2	2·62			
„ „ „ 3	3·08	2·73	1·28	2·72
„ „ „ 4	2·64			
„ „ „ 5	3·4			
Uninoculated native No. 1	0·57			
„ „ „ 2	1·47	1·2	0·94	1·26
„ „ „ 3	1·86			
„ „ „ 4	0·90			
Uninoculated native No. 1	1·92			
„ „ „ 2	1·16			
„ „ „ 3	1·66	1·93	1·94	1·84
„ „ „ 4	2·12			
„ „ „ 5	1·7			
„ „ „ 6	3·04			
A. E. W.	4·5			
W. P. M.	3·5	3·74	4·48	4·1
F. C. L.	3·23			

When it is desired to compare the effect of pooling after incubation with pooling before incubation, we leave behind on the slide, when filling in our first pipette, enough of our phagocytic mixtures for filling in a second. Into this second pipette we take up, as before, an equal volume of each phago-

cytic mixture; but we now immediately blow them out so as to form a common drop; and then, after mixing, draw them up into the pipette—obtaining in this way the equivalent of an experiment with a pooled serum.

On referring to Table VIII (*supra*, p. 75) and comparing columns 3 and 5, it will be seen that we obtain by pooling the phagocytic mixtures after incubation values which show an all but exact correspondence with the values obtained by averaging the phagocytic counts obtained when the constituent sera are separately tested. And it will be seen on referring to column 4 of this table and to column 3 of the foregoing table, that we obtain with phagocytic mixtures pooled before incubation just such results as are obtained with pooled sera.

PHAGOCYTO-BACTERICIDAL POWER

Reverting to the line of thought we were pursuing before entering upon the above excursus, we now pass on to consider yet another antibacterial attribute of the blood. We have seen that the data furnished by measurements of the pneumo-opsonic power were not sufficiently consistent from one day to another to allow of their being employed for the selection of the optimum dose of pneumococcus vaccine. This made us cast about for some other method of blood-examination which should be competent to do what the measurement of the opsonic index had failed to do. In this way we came upon the method which is here to be described. We may, for reasons which will presently appear, designate it by the name of the "phagocyto-bactericidal method."

With regard to this method we may point out at the very outset, that while it will, as it seems to us, help to illuminate the darkness which covers the mechanism of the destruction of microbes in the organism, we recognise that it would be difficult to apply on a large scale outside the four walls of a laboratory. For this reason, and because by the time that we had alighted upon the method our laboratory investigations were drawing to a close, and also because we had already obtained from the opsonic method sufficient information to allow of our

now pursuing our investigations, so far as they related to prophylaxis, by the method of mass-experiments, we did not ourselves employ the phagocyto-bactericidal method for the determination of the optimum dose of vaccine.

What pointed the way to the investigation of the phagocyto-bactericidal power of the blood was the fact that we had failed to find in the films which came under close inspection in connexion with our opsonic measurements any indication of an intracellular digestion of pneumococci in the phagocytes.

It was natural to pursue these observations by making cultivation experiments, employing in these the looped pipettes with the original bactericidal technique already referred to. On actually making experiments we found, with absolute uniformity, that there does not occur in the ordinary phagocytic mixture any destruction of pneumococci, even when the microbes are left in contact with the serum and corpuscles for as long as twenty-four hours.

It immediately suggested itself to employ the modified bactericidal technique, which permits of working with practically undiluted blood[1] (*vide* pp. 61 and 62 *supra*), and to experiment with (*a*) unaltered blood issuing direct from the capillaries; (*b*) defibrinated blood—i.e. leucocytes and serum obtained by stirring up the clot in an ordinary blood capsule; (*c*) human and horse blood in which clotting had been deferred by the action of cold; (*d*) decalcified and recalcified bloods; (*e*) plasma separated from the unaltered blood by rapid centrifugalisation; and (*f*) the residue of corpuscles which remains over after pipetting off the plasma. We propose elsewhere to treat fully of the results of these and other experiments. We accordingly set down here only what is fundamental and what relates specifically to the problem of the natives' defective resistance against pneumococcic infection.

[1] It may be explained that the fact of the blood clotting in the capillary stem is, from the point of view of that technique, perfectly indifferent.

The following experimental results seem to us from these points of view specially deserving of attention :—

(1) We find that when blood fresh from the capillaries operates upon the pneumococcus it invariably kills quite large numbers of pneumococci. We have obtained in this way with our own bloods a destruction of pneumococci equivalent to a destruction of 600,000, and on one occasion to 1,000,000 pneumococci, by 1 c.c. of blood.

(2) In connexion with the staphylococcus—a microbe which is not destroyed either by undiluted serum nor yet by the serum and white blood corpuscles in the ordinary phagocytic mixture—a bactericidal effect, but on a much smaller scale than that with the pneumococcus, is obtained by the operation of the unaltered blood.

(3) In experiments made by our fellow-worker, Captain S. R. Douglas, in which serum and unaltered blood were respectively brought to bear in conjunction with leucocytis upon the tubercle bacillus, a definite bactericidal effect was obtained with the whole blood, but not with the serum. There remains, however, to be studied in connexion with the tubercle bacillus—for the results obtained with it have not been uniform—the influence exerted by the age and strain of the culture and by the length of exposure to the action of the blood.

(4) No bactericidal effect upon the pneumococcus is exerted by the plasma which has been separated by centrifugalisation from the unaltered blood.

We conclude from this that the phagocytes are an essential factor in the bactericidal action of the whole blood, and that action is a phagocyto-bactericidal action.

(5) With the corpuscles and serum of defibrinated blood, and with the decalcified blood we have obtained practically no bactericidal effect. We obtained some bactericidal effect with recalcified blood.

We infer from this that contact with the unaltered plasma, or possibly the chemical change associated with

blood coagulation,[1] is an essential factor in the destruction of the microbes.

(6) We obtained no bactericidal effect with either human blood or horse blood which had been cooled over ice.

(7) While we obtained in a uniform manner with our own unaltered bloods a destruction of considerable numbers of pneumococci, we did not in four series of experiments carried out on uninoculated and inoculated Tropical Natives obtain in any instance any considerable phagocyto-bactericidal effect upon the pneumococcus.

Excursus No. II.—On the Racial Differences between the Tropical African Native and the European with respect to the Antibacterial Effect which their Bloods exert upon the Pneumococcus.

We have in the course of the foregoing study of the antibacterial effects exerted by the blood upon the pneumococcus, made frequent reference to the fact that the antibacterial power of the native bloods was less than that of our own bloods. Seeing that we have perhaps here the explanation of that high incidence-rate and great fatality of pneumonia, pneumonic cerebrospinal meningitis, and other pneumococcic infections among African Natives congregated upon the Rand and elsewhere in labour-camps and compounds, it will perhaps be of interest to gather together the results of the observations which we made in the course of our work on the differences between Native and European bloods.

We found in our study of the bactericidal and growth-inhibiting powers of the serum only slight indications of a difference between the sera of the African Native and the European. If there was such a difference, the advantage lay with the European.

In connexion with our measurements of the opsonic power of the blood, there was no longer any possibility of doubt. Here, as will be seen from the results collected into the subjoined table, very distinct differences emerged.

[1] It will be remembered in this connexion, on the one hand, that the exudation clots in the alveoli of the pneumonic lung; and, on the other hand, that enormous numbers of pneumococci are killed off in that exudation.

TABLE IX

Showing the Pneumo-opsonic Indices obtained by dividing in each case the arithmetical mean of the phagocytic counts of a group of Europeans (laboratory workers), with the average phagocytic count[1] of a group of Uninoculated Tropical African Natives.

Serial number of the strain of pneumococcus employed.	Number of experiments undertaken with it.	Opsonic indices of groups of uninoculated natives.
83	4	0·8, 0·7, 0·5, 0·2
92	28	0·1, 0·1, 0·2, 0·3, 0·2, 0·4, 0·3, 0·4, 0·1, 0·4, 0·3, 0·3, 0·4, 0·4, 0·6, 0·25, 0·4, 0·9, 0·7, 0·4, 0·3, 0·4, 0·6, 0·2, 0·5, 0·4, 0·9, 0·7
135	2	1·0, 0·8
165	11	0·8, 0·8, 1·0, 0·5, 0·6, 0·6, 0·6, 0·8, 0·9, 0·9, 1·1
19	1	0·2
172	1	1·1
77	1	0·4
131	1	0·4
9	1	1·0
174	1	0·3
52	1	1·2
96	1	1·2
38	1	0·44

The findings which are set forth in this table and its teaching may be summarised as follows :—

With eight of the thirteen strains of pneumococcus which were tested, the sera of the uninoculated Tropical Natives (it will be remembered that a certain number of infected natives must have been included among our uninoculated) gave opsonic indices of less than one, and generally of much less than one.

With the remaining five strains the sera of the uninoculated Tropical Natives gave indices of one or a little above or below one.

The strains which brought out differences as between Tropical Natives and Europeans were in all cases virulent strains, in the sense that when originally isolated they failed to give phagocytosis ; and could only, by repeated cultivation on artificial media and suspension in water, be brought into a condition to give phagocytosis. Moreover—and the significance of this will not be missed—when these strains began to

[1] This count was obtained by pooling, in accordance with the technique described in Excursus No. I, the phagocytic mixtures of the group after these mixtures had been separately incubated.

Table X

Showing the Results of a Comparison between the Staphylo-opsonic Power of Europeans and Tropical African Natives.

Observation No. 1.		Observation No. 2.		Observation No. 3.		Observation No. 4.	
Indication of the source of the blood.	Phagocytic count.	Indication of the source of the blood.	Phagocytic count.	Indication of the source of the blood.	Phagocytic count.	Indication of the source of the blood.	Phagocytic count.
A. E. W. ..	1·87	A. E. W. / W. P. M. / F. C. L. } pooled serum*	68	A. E. W. / W. P. M. / F. C. L. } pooled serum*	2·74	W. P. M. ..	4·12
W. P. M. ..	2·28						
Native No. 1	2·16	Natives, Group No. 1,† pooled serum	2·1	Native No. 1 ..	3·3	Native No. 1	3·96
,, ,, 2	2·02			,, ,, 2 ..	4·72	,, ,, 2	3·88
,, ,, 3	2·73	Natives, Group No. 2, pooled serum	1·86	,, ,, 3 ..	3·64	,, ,, 3	4·88
,, ,, 4	2·81						
,, ,, 5	2·0						
,, ,, 6	2·1						
,, ,, 7	2·58	Natives, Group No. 3, pooled serum	2·72				
,, ,, 8	1·91						
		Natives, Group No. 4, pooled serum	1·9				

* It will be remembered that it has been shown in Excursus No. I *supra*, that when dealing with normal bloods the phagocytic count of the pooled serum is equivalent to that of the highest of the constituent sera.

† This and the following groups consisted of 4 to 6 natives.

give phagocytosis, they in every case gave it, at first, only with European sera. After a time they began gradually to give it also with the sera of uninoculated Tropical Natives. The fact that strain No. 92 continued for a long time to differentiate sharply between Native and European bloods, is we think due to our having nearly always grown this strain on agar made up with unheated blood.

With regard to the strains of pneumococcus which failed to bring out differences between Native and European bloods these were presumably non-virulent strains. They were, at any rate, either strains which gave phagocytosis immediately on isolation from the patient, or strains which had been sub-cultured without special precautions for a long time outside the body.

Compressing all the above into a sentence we may say that the teaching of the table resolves itself into this : that, where in connexion with the pneumococcus a difficult task is set to the blood, the Native is far behind the European ; but that, where an easy task is set, he draws up level.

Having considered the facts which relate to the uninoculated native, we have now to carry our thoughts back to those which relate to the native who is making immunising response to inoculation or auto-inoculation ; and to ask ourselves what is the precise significance, for the problem here under discussion, of the observation that it is only exceptionally that the opsonic index of the native who is making immunising response comes up to the arithmetical mean of the pneumo-opsonic indices of the Europeans who served as controls in these measurements.

The full significance of this fact comes home to us only when we realise that it is, not so much the original content of a patient's blood in protective substances, as his capacity for generating these in response to microbic invasion which gives the measure of his power of combating infection.

Once this principle has been grasped it becomes clear that there is furnished to us, in the comparison between the opsonic power of the normal white man and that of the native who is making active immunising response, a better measure of the native's defect of resistance than is afforded by the comparison between the opsonic power of the normal white man and that of the normal native.

But there will perhaps here suggest itself the question as to whether there is really anything to indicate that the correlation between the native's relatively low opsonic index and his relatively high susceptibility to pneumococcus infections

is not an accidental association. A comparison between the native's opsonic power to staphylococcus with that of the white man would go far to settle this point. For by common consent the native is a good 'subject for operation'—probably a better subject than the European. This is as much as to say that the native offers good resistance to the common microbes of wounds—a state of things which ought, if there be a causal correlation between the opsonic power of the blood and the power of fighting a microbic infection, to go together with a satisfactory opsonic index. We made this almost critical investigation, repeating it four times, with the results which are set forth in Table X (*supra*, p. 81).

The above results clearly lend very strong confirmation to the view that the Native's deficiency in pneumo-opsonic power does stand in some causal relation with his low resisting power to pneumococcic infections.

Finally it would be difficult to doubt that we have in the defect of pneumophagocyto-bactericidal power to which attention was called above a native character which stands in direct causal relation to the ravages which the pneumococcus makes among them.

SECTION IV

ACCOUNT OF THE MASS-EXPERIMENTS WHICH WERE INSTITUTED TO TEST THE EFFICACY OF VACCINE-THERAPY AND PROPHYLACTIC INOCULATION AGAINST PNEUMONIA

We have now completed the setting forth of the work which we did in connexion with the investigation of the antibacterial effects exerted by the blood upon the pneumococcus, and the testing and improvement of the methods for measuring it.

We now go on to consider the results which were obtained when we passed from laboratory work to actual phylactic and prophylactic inoculation.

We may begin with the former.

TREATMENT OF PNEUMONIA BY VACCINE-THERAPY

It will be well to realise at the outset under what disabilities of ignorance we here pursued our work. The methods of blood examination which so often disappointed

us when we were endeavouring to compare from day to day the opsonic power of the inoculated with that of the uninoculated natives, left us quite in the lurch when we set ourselves to make similar daily measurements in the case of our pneumonia patients. We were unable to trace upon the fifty immunisation curves which we plotted out in connexion with this work the effect of the doses of vaccine which we administered.

Accordingly, from first to last, we had to guide ourselves in our choice of doses, and of the intervals between our doses, only by *a priori* considerations, and by the uncertain and flickering light which is furnished by temperature charts and the clinical symptoms. Influenced by the anticipation that the infected natives would be much more sensitive to pneumococcus vaccine than the uninfected native, we employed only doses of $2\frac{1}{2}$ to 50 millions of pneumococci; and we conformed to the principle of giving in the less serious conditions larger, and in the more serious ones smaller, doses. In the ordinary case we repeated the dose at intervals of twenty-four to forty-eight hours.

These experiments—they have only the value of properly controlled reconnoitring experiments — were carried out in the hospital of the W.N.L.A. on Tropical Native patients. Many of these were, when admitted to hospital, already in an advanced stage of pneumonia. We accepted for our experiments only those who presented quite typical physical signs, and these were taken for treatment by vaccine-therapy, or for treatment by the expectant method, alternately, and strictly in the order in which they were admitted to hospital. We took for every uninoculated patient who was treated by vaccine-therapy an uninoculated control, and for every inoculated patient an inoculated control.

As the net effect of our treatment, we obtained the results which are set out in the subjoined table.

TABLE XI

Showing the Case-Mortality of Pneumonia in Tropical Natives treated respectively by repeated small doses of Pneumococcus Vaccine and by Expectant Treatment.

Therapeutic methods employed.	Number of cases.	Number of deaths.
Vaccine-therapy	159	.. 50
Expectant treatment	149	.. 48

We would in connexion with these results specially emphasise (1) that they apply only to Tropical Natives who having a very low power of resistance have contracted virulent infection ; and (2) that they apply only to inoculations carried out on such Natives with the doses specified above.

What we have to say in connexion with the prospects of therapeutic inoculation in pneumonia will be better deferred till we come to summarise and comment upon the results obtained by inoculation (*infra*, pp. 98 and 100).

PROPHYLACTIC INOCULATION AGAINST PNEUMONIA

We pass now to study the results which were obtained by prophylactic inoculation. The inoculations which we carried out or initiated range themselves under six mass-experiments.

Mass-experiment No. 1

This mass-experiment was undertaken in the compound of the Witwatersrand Native Labour Association. This compound, familiarly known as the W.N.L.A. Compound, is, as has already been briefly explained, the receiving station at Johannesburg where the gangs of Native labourers, who are recruited for the general service of the mines, are housed for three to four weeks before they are drafted off to their respective mines.

We confined our operations in this and the four next mass-experiments to the Tropical Natives. For it is especially these who are ravaged by pneumonia.

In each case, two or three days after the arrival of a new gang, the natives were lined up. We then, dismissing any who showed symptoms of illness, inoculated as they filed past us every alternate man, reserving in this way half of each gang to serve as controls.

As the men came up to us, the inoculated were made to pass on one side, and the uninoculated on the other; and lists were made of the depot numbers of the two groups—each man's identification docket being at the same time ruled across with a diagonal line, which was red or blue according as he was inoculated, or reserved as a control.

After the lapse of eight to ten days the natives were again ranged up, and every man who had on the first occasion been inoculated was now reinoculated, while the controls were still kept as controls. The red or blue diagonal line on each man's docket was at the same time converted into a red or blue cross; and a corresponding entry was made upon the lists.

Proceeding in this manner between the months of October, 1911, and April, 1912, with each gang of Tropical Native labourers as it arrived, we inoculated a total of 5963 and reserved 5671 to serve as controls.

The doses which were employed varied with each gang and sub-group—for we were, as has been indicated above, engaged in following out from day to day the effect exerted on the blood by different doses and different schemes of administration.

The average amount of vaccine given in the two successive inoculations taken conjointly was something like 300 millions of pneumococci. It in no case exceeded 600 millions.

The results of the inoculations are furnished, so far as relates to the three or four weeks dating from the first inoculation, in the register of pneumonia cases and deaths kept in the hospital attached to the W.N.L.A. Compound. The clinical diagnosis was in each case made

by the Medical Officer, Dr. George A. Turner, or the Assistant Medical Officer, and by one of us (W. P. M.). In the fatal cases the cause of death was controlled by post-mortem examination carried out by the Medical Officer.

Information with regard to the subsequent history of the inoculated and uninoculated is furnished in two sets of returns.

We have, first, the special monthly returns made to us from the mines—the so-called *red and blue monthly returns*. These record the number of cases of pneumonia and deaths from pneumonia occurring respectively in the red and blue group of Tropical Natives.

We have, secondly, the returns of deaths, and specifically of deaths from pneumonia, rendered thrice monthly from the mines to the Chamber of Mines for the information of Government.

The 'red and blue' returns proved unserviceable for our purpose, inasmuch as the depot numbers of those who contracted, and died from, pneumonia were not supplied; and also because the results applying to the separate gangs were not kept apart.

The Governmental returns, since they furnish the depot numbers of those who succumbed to pneumonia, are those we depend upon for the later results set forth in the table below. The results of the mass-experiment, ascertained as explained above, are as follows :—

TABLE XII

Showing the Number of Pneumonia Cases and Deaths from Pneumonia which occurred in the W.N.L.A. Compound between the date of the first Inoculation and the Departure of the Natives to the Mines.

	Number of men in the group.	Cases.		Deaths.	
		Number.	Percentage.	Number.	Percentage.
Inoculated	5963	147	2·6	50	0·83
Uninoculated	5671	198	3·5	87	1·53

Table XIII[1]

Showing the number of Deaths from Pneumonia reported from the Mines in each successive month

	Number of men in the group.	Second month.	Third month.	Fourth month.	Fifth month.	Sixth month.
Inoculated	5963	11	19	12	10	7
Uninoculated	5671	29	19	15	13	8

It will be seen that the inoculation exerted a marked effect for two months, but that after the end of the second month the inoculated had no advantage over the uninoculated.

To obtain the measure of the total effect of inoculation on the death-rate from pneumonia we may combine the figures for the deaths in Tables XII and XIII.

Table XIV

Showing the Effect which was exerted upon the Death Rate from Pneumonia in the first two months after Inoculation.

	Number of men in the group.	Deaths.	
		Number.	Percentage.
Inoculated	5963	61	1
Uninoculated	5671	116	2

Mass-experiment No. 2

After Mass-experiment No. 1 had been in progress for a certain time, and after it had appeared from the returns that favourable results were being obtained, we endeavoured to procure larger figures, such as would be really serviceable for statistical purposes, by undertaking ‘general inoculations’ at the mines.

We accordingly in December, 1911, and January, 1912, organised and ourselves took part in a number of ‘general inoculations’ at the Mines, and Dr. Turner, who helped

[1] In compiling this table the fact that the native whose death was recorded in the Report from the Mines had passed before us, and had been inoculated or set aside as a control, was verified by reference to our records; the period which had elapsed since the date of the first inoculation and his death being at the same time ascertained.

us in this work, afterwards took independent charge of a number of others.

We compute that in all 20,000 to 30,000 natives were in this way inoculated.

Our intention was that the inoculated and the controls should, in connexion with these inoculations, have been chosen and registered in exactly the same way as had been done in the W.N.L.A. Compound ; and we arranged for a special form of return in which the population of the mines should be divided up into (*a*) inoculated natives, (*b*) natives who were set aside as controls, and (*c*) natives who were excluded from the experiment either because they had joined later, or because they had for other reasons failed to put in an appearance at the inoculation parade.

All sorts of difficulties, however, presented themselves in connexion with working out this scheme.

It was found very difficult to get the records of the inoculated and controls accurately made when such large bodies of natives as were here in question were being dealt with.

Again the arrangements made for keeping track of the inoculated and uninoculated left in many places very much to be desired.

Complications also presented themselves with regard to making proper allowance for natives who left the mines ' time-expired ' within the period of observation.

Lastly, the inoculated turned out to be non-homologous with the controls, and there was—in contrast with what obtained in our other experiments—a sensible defect of homogeneity in the population of natives we were dealing with.

In connexion with the comparability of the inoculated and the controls it may be explained that the Native labourers on the Rand come from as far south as the Cape, and from as far north as the Equator ; and that there are between the different races of natives at the

mines great differences with respect to tractability and susceptibility to pneumonia—the Tropical Natives being at once the most tractable and the most susceptible to pneumonia ; and the East Coast Natives, as we are informed, much more difficult to handle, and at the same time more resistant to pneumonia.

It will be readily understood that under these circumstances the inoculated group would tend to be more largely composed of the more tractable and, as it happens, more susceptible Tropical Natives ; and the uninoculated group to be composed of the less tractable and, as it happens, less susceptible East Coast Natives.

In connexion with the homogeneity of the population operated upon, it is to be observed that the fresh arrivals are (as will be seen from the figures for the uninoculated in Tables XII and XIII, XV and XVII) the most susceptible to pneumonia, and that those who have been longer upon the mines have become more resistant to pneumonia. By consequence every group which is chosen from the native population, without reference to length of residence on the mines, will comprise persons of very different degrees of resistance.

As soon as these considerations had, one after the other, come home to us, we decided to bring this particular mass-experiment to a close, and to jettison, as open to fallacy, such statistical returns as had already been sent in to us in connexion with the experiment.

If, as we cannot in view of our other experience doubt, this mass-experiment gave good results we suggest that the advantage was reaped in the form of a diminution in the general death-rate from pneumonia on the Rand.

Mass-experiment No. 3

Having learned from experience in Mass-experiment No. 2 the difficulties which have to be confronted and the fallacies which have to be avoided in connexion with a general inoculation, we set ourselves to organise such

an experiment upon better lines. The mass-experiment here in question was begun in May, 1912. It consisted in a series of general inoculations undertaken in twenty mines[1] and limited to Tropical Natives who had, in the season 1911–12, passed out to the mines from the W.N.L.A. Compound. In view of the fact that it had been shown in Mass-experiment No. 1 that there was, after two months, no difference between inoculated and uninoculated, the whole of the Tropical Natives of the year, with the exception of those few who left the compound for the mines in March and April,[2] were regarded as, for our purposes, homologous.

In each mine three general inoculations were undertaken, approximately a month intervening between the first and the second, and again between the second and the third inoculation; and the dose of vaccine was uniformly 150 million pneumococci.

On the *first* occasion approximately half of the Tropical Natives were inoculated, and half were left as controls—giving a group of 3975 inoculated and a group of 4769 uninoculated. Among these last were counted in a certain number who were actually at work on the mine, but who for one reason or another were not actually forthcoming at the first parade.

At the *second* general inoculation, half of those who had on the first occasion served as controls were inoculated; and of those who were on that occasion inoculated one moiety was reinoculated, while inoculation was withheld from the other, with a view to find out how long the effect of the previous inoculation would make itself felt.

At the *third* general inoculation, again, half of those who functioned at the second inoculation as controls were inoculated; and nearly all those who were previously inoculated were reinoculated.

[1] The mines chosen for the experiment were those which had received the largest number of Tropical Natives.

[2] These were excluded from the experiment and left out of the record.

Quite special care was devoted to ensuring accuracy in the records—the procedure adopted being as follows: For each mine two lists were prepared. On the first (hereafter called the 'depot list') the 'depot numbers,' with which the natives leave the W.N.L.A. Compound, were arranged in serial order, the corresponding 'mine numbers,' which are given to the natives on arrival at their mines, being entered in the second column. On the second list (hereafter called 'the mine list') the mine numbers were set down in serial order, and the corresponding depot numbers were entered in the second column. This done the depot list was taken in hand by us, and we inserted in the third column, opposite the numbers, alternately a red or a blue diagonal line—the red line to indicate that the native was to be inoculated, the blue that he was to serve as a control. Corresponding entries were then made on the mine list.

When visiting the mine for the purpose of the general inoculation the natives were identified by their mine numbers as they passed up from their work, and they were inoculated or sent on uninoculated, according as their numbers were marked in red or blue, and the diagonal lines on the list were at the same time converted into crosses to show that these natives had been dealt with. Corresponding crosses were afterwards made upon the depot list.

The returns were made monthly by the Medical Officers of the mines on printed forms specially issued for this purpose. The return gave in connexion with each patient admitted to hospital his depot number, the date of his admission, the diagnosis, and the date of his discharge or death.

In the table given below we have grouped the results under the headings of results in the *first*, *second*, *third*, and *fourth* months.

We have included in the results obtained by inoculation in the first month, not only the results which refer to

the 3975 inoculated in the first general inoculation, but also the figures which refer to the natives who were inoculated for the first time at the second and third general inoculations. Moreover, in the case where a man was inoculated more than once we have set down in the 'results obtained in the first month after inoculation' those which apply to him for the month following each of his several inoculations. For we find by analysis of the figures that the inoculation of men who have been inoculated one month previously with 150 millions gives neither better nor worse results than are obtained where men are inoculated for the first time.

We have dealt in a precisely similar fashion with the results which apply to the uninoculated. For instance, when in making up our results for the first month, we come upon a man who was at each of three successive general inoculations taken as a control, we enter him in our statistics three times over (once for each several month) in order that he may serve as a control for the men who were inoculated at the first, second and third inoculations respectively. Similarly when we come upon a man who was inoculated for the first time at the third general inoculation, we include him twice over in our controls. And when we come upon a man who was inoculated for the first time at the second general inoculation, we include him once in our controls. We follow, *mutatis mutandis*, precisely the same procedure when dealing with the returns which apply to the second, third and fourth months.

It will be seen that with the very small dose of vaccine which here came into application a very striking advantage was achieved in the first month after inoculation, but that advantage had nearly passed away by the end of the third month. The records are not continued beyond the fourth month because the mass-experiment next on our list was then begun.

TABLE XV

Showing results for Four successive Months after Inoculation.

	Number of men in the group.*	Cases of pneumonia. Number.	Cases of pneumonia. Percentage.	Deaths from pneumonia. Number.	Deaths from pneumonia. Percentage.
Results for the First Month					
Inoculated	10,626	125	1·1	22	0·21
Uninoculated	10,508	216	2·05	40	0·38
Results for the Second Month					
Inoculated	6787	76	1·12	15	0·22
Uninoculated	8380	128	1·5	25	0·3
Results for the Third Month					
Inoculated	6103	59	0·96	13	0·21
Uninoculated	7823	92	1·2	22	0·28
Results for the Fourth Month					
Inoculated	6103	44	0·72	16	0·26
Uninoculated	7823	68	0·87	20	0·25

* In view of the fact that the corrections which would be applicable under the heading of deaths and repatriations would be quite insignificant, we have not troubled to deduct them from the numbers of the inoculated and uninoculated.

Mass-experiment No. 4

This experiment consisted in a general inoculation carried out, in November, in eighteen out of the twenty mines which were in question in the last experiment. It relates to those Tropical Natives who belonged to gangs which passed through the W.N.L.A. Compound in 1912, and who were accordingly due to remain in the mines till at least the end of January, 1913. Those who had in the last experiment served as controls were retained as such, and the rest were reinoculated—in each case with a dose of 1000 millions of pneumococci, grown in part on serum broth, and in part on glucose serum broth. In this way there was obtained a group of 610 uninoculated, which for the purpose of such comparisons as those we are here making was undesirably small, and a group of 2322 inoculated. The results as ascertained from the returns rendered on the printed forms referred to in connexion with the last experiment were as follows :—

TABLE XVI

Setting forth the Results obtained for the Period of Five Months after the date of the Inoculation

	Number of men in the group.	Cases of pneumonia.		Deaths from pneumonia.	
		Number.	Percentage.	Number.	Percentage.
Inoculated	2322	70	3·0	20	0·86
Uninoculated	610	21	3·4	8	1·3

The question as to why larger advantage was not here reaped from inoculation is reserved for discussion in our summary of results (Section V, *infra*).

Mass-experiment No. 5

This experiment was undertaken upon the Tropical Natives who arrived in the Compound of the W.N.L.A. between the middle of August and the end of November, 1912.

The chief objects that it had in view were: (*a*) the determination of the optimum dose of pneumococcus vaccine for prophylactic uses, and (*b*) the decision of the question whether cultivations on glucose serum broth furnished a better vaccine than cultures on the ordinary serum broth.

The inoculations were carried out exactly as in the case of Mass-experiment No. 1, with the difference that only every fifth native was taken as a control.

The procedure adopted with regard to dosage was to take for the general inoculation in each case doses which had been previously ascertained to be perfectly safe; and then to reconnoitre by inoculating a small group with larger doses.[1]

[1] We found in these experiments that doses up to 40,000 millions of pneumococci produced nothing more than a very slight constitutional disturbance and a very small rise of temperature. This is in good accord with the generalisation (*vide supra*, Section II) that what counts in the case of an inoculation is not the actual quantum of vaccine we incorporated; but the quantum of antigen set free from it in the organism of the patient.

Advancing in this manner we obtained for study a series of six groups.

The general results may be summarised as follows : Employing a *vaccine prepared by cultivating the pneumococcus on blood broth* and a dose of 250 millions, we obtain, for a period of one month after inoculation, a reduction of the incidence from 7 per cent in the controls to 3·7 per cent in the inoculated ; and a reduction of the death-rate from 2·9 per cent in the controls to 1·5 per cent in the inoculated, that is to say, in each case a reduction equivalent to about 50 per cent. With a dose of 500 millions of the same vaccine we obtain, for the first three months after inoculation, a reduction of about 25 per cent in the incidence and nearly 50 per cent of the death-rate. With 1250 millions of the same vaccine we obtain a much less favourable result : a reduction, on a period of three months, of 30 per cent in the incidence, and of only 20 per cent in the death-rate. We may presume that the dose here employed was too large. Employing *a vaccine prepared by cultivating a pneumococcus on glucose blood broth* we obtain, for a period of two months, with a dose of 500 millions a reduction of 50 per cent in the incidence, and of 40 per cent in the death-rate. With a dose of 1000 millions we obtain, over a period of three months, a reduction of 30 per cent in the incidence, and of over 60 per cent in the death-rate. With a dose of 2500 millions we again obtain less satisfactory results ; a reduction of just over 20 per cent in the incidence, and a reduction of 35 per cent in the death-rate.

There can be extracted from the statistical data which are available in connexion with this mass-experiment, not only conclusions bearing on the question of the relative efficacy of the various doses of vaccine which were administered, but also valuable information bearing on the question of the production of a negative phase—information which has, as we shall see, an important bearing on the question of the utilisation of vaccine in the treatment of pneumonia.

Table XVII[1]

Showing the results obtained by the Inoculation of various doses of Pneumococcus vaccine grown on blood broth and glucose blood broth respectively.

	Number of men in the group.	First Month.		Second Month.		Third Month.		Fourth Month.		Fifth and Sixth Months.	
		Cases.	Deaths.	Cases.	Deaths.	Cases.	Deaths.	Cases.	Deaths.	Cases.	Deaths.
(A) *Results obtained by the Inoculation of* 250 *millions of Pneumococci grown on blood broth.*											
Inoculated	646	24	10	17	5	14	4	9	2	16	5
Uninoculated	626	44	17	17	5	12	4	15	5	16	6
(B) *Results obtained by the Inoculation of* 500 *millions of Pneumococci grown on blood broth.*											
Inoculated	759	25	8	16	4	17	2	14	4	19	8
Uninoculated	764	46	19	21	6	17	5	18	5	20	6
(C) *Results obtained by the Inoculation of* 1250 *millions of Pneumococci grown on blood broth.*											
Inoculated	1582	37	17	40	10	28	10	17	6	44	13
Uninoculated	791	23	10	31	8	21	6	12	3	14	7
(D) *Results obtained by the Inoculation of* 500 *millions of Pneumococci grown on glucose blood broth.*											
Inoculated	463	18	10	7	1	9	3	7	2	7	5
Uninoculated	457	35	14	14	5	10	3	12	4	10	4
(E) *Results obtained by the Inoculation of* 1000 *millions of Pneumococci grown on glucose blood broth.*											
Inoculated	650	20	6	20	3	10	2	6	3	14	3
Uninoculated	595	37	16	18	6	15	4	15	4	14	4
(F) *Results obtained by the Inoculation of* 2500 *Pneumococci grown on glucose blood broth.*											
Inoculated	1582	47	17	42	8	28	5	21	10	35	8
Uninoculated ..	791	23	10	31	8	21	6	12	3	14	7

[1] It is to be observed that the results of those inoculated with reconnoitring doses are excluded from consideration, and that the uninoculated who serve for controlling the effect of one dose are often the selfsame individuals as serve for the controlling of another dose.

The data which seem to us important from this point of view are set out below in Table XVIII.

The facts which are set forth in this table are, as will be seen, very remarkable. Associating together the figures which apply to Groups A, B, D, and E : i.e. the groups which received doses up to 1000 millions of pneumococci, we find that, in the first four days after inoculation, 2500 inoculated had an incidence-rate of 0·52 per cent, and a death-rate in connexion with these cases of 0·16 per cent ; while 750[1] controls had an incidence-rate of 1·4 per cent, and a death-rate in connexion with these cases of 0·84 per cent. In other words, the uninoculated had an incidence-rate nearly three times, and a death-rate five times greater than the inoculated.

Again, associating together the figures which relate to Groups C and F—groups which received doses of over 1000 millions of pneumococci—we find that 3200 inoculated had for the same period an incidence-rate of 1·1 per cent, and a death-rate in connexion with these of 0·32 per cent, while 800 controls had an incidence-rate of 0·4 per cent, and a death-rate also of 0·4 per cent.

Two important conclusions follow : the *first* is that pneumococcus inoculation undertaken with doses up to 1000 millions had a marked effect in aborting pneumonia, and in diminishing the case mortality. Or we may phrase it otherwise. Vaccine-therapy as applied to the treatment of pneumonia is successful when doses of 250 to 1000 millions are given in the incubation stage of the disease. The *second* conclusion is that inoculation undertaken with doses of over 1000 millions of pneumococci may perhaps temporarily increase the incidence-rate of pneumonia.

It is perhaps of interest to point out that these conclusions are essentially the same as those formulated in connexion with plague vaccine by Mr. Haffkine. And

[1] This figure is arrived at by taking the actual number of men who served as controls for groups A, B, D, and E.

Table XVIII

	Number in group.	Number of cases of pneumonia which developed.													
		First Day.		Second Day.		Third Day.		Fourth Day.		Fifth Day.		Sixth Day.		First Six Days.	
		Cases.	Deaths.	Cases.	Deaths.	Cases.	Deaths.	Cases.	Deaths.	Cases.	Deaths.	Cases.	Deaths.	Cases.	Deaths.
Group A (inoculated with 250 millions)	646	—	—	—	—	1	1	2	1	—	—	—	—	3	2
Control group	626	1	1	4	1	3	1	2	2	—	—	2	2	12	7
Group B (inoculated with 500 millions)	759	—	—	2	—	1	1	—	—	3	1	1	—	7	2
Control group	764	1	1	5	2	3	1	2	2	—	—	2	2	13	8
Group C (inoculated with 1250 millions)	1582	8	4	2	—	1	1	1	—	—	—	—	—	12	5
Control group	791	1	1	2	2	—	—	—	—	—	—	1	—	4	3
Group D (inoculated with 500 millions glucose vaccine)	463	1	1	—	—	1	—	—	—	—	—	—	—	2	1
Control group	457	1	1	3	1	3	1	1	1	—	—	2	2	10	6
Group E (inoculated with 1000 millions glucose vaccine)	650	—	—	1	—	2	—	2	—	—	—	1	—	6	—
Control group	595	1	1	4	2	3	1	1	1	—	—	2	2	11	7
Group F (inoculated with 2500 millions glucose vaccine)	1582	7	3	11	2	1	1	3	—	2	2	—	—	24	8
Control group	791	1	1	2	2	—	—	—	—	—	—	1	—	4	3

the view that Mr. Haffkine maintained (in contravention to the *a priori* view held by the writer) that plague vaccine does not produce a negative phase, and that it has the power of aborting an incipient attack, was afterwards established by evidence accumulated by Miss Alice Corthorn, M.D.,[1] and Surgeon-General Bannermann, I.M.S.[2]

In connexion with this all that requires to be said is that the generalisations in Section II of this Report—generalisations which have been reached only after years of further work—have made it intelligible that a negative phase should manifest itself with large doses of typhoid vaccine, a vaccine which is easily broken down in the normal organism, and again with all vaccines after the organism has, by foregoing immunising response, acquired bacterioclastic power, and that this phase should make default in the uninfected organism, and in the early stages of infection when vaccines, such as plague vaccine and pneumococcus vaccine which are with difficulty broken down in the body, are inoculated.

In concluding this account of the results obtained in Mass-experiment No. 5 we may profitably advert to one more general consideration. It is, as will presently be brought out more fully in Section V, reasonable to expect that an effective inoculation will give an additional bonus in the form of a diminution in the morbidity which comes upon the record under the heading of "Other Diseases." In point of fact the records which relate to the particular mass-experiment we are here discussing show such a reduction. We have our bonus in the form of a 15 per cent reduction in the 'other diseases' of the inoculated, the figures being: *inoculated*, 6224; *uninoculated*, 1545. Cases of sickness other than pneumonia: in *inoculated*, 2154; in *uninoculated*, 620.

We now pass to our sixth and last mass-experiment.

[1] *Brit. Med. Jour.*, Jan. 25, 1902. [2] *Ibid.*, Sept. 14, 1901.

Mass-Experiment No. 6

This mass-experiment was undertaken upon the natives employed in the Premier Diamond Mine—a mine which, despite the fact that it employs no Tropical labour, has always suffered very severely from pneumonia.

We began with a general inoculation on January 21, 1912, inoculating at a sitting about four thousand natives.

The experiment thus begun was followed up by a methodical inoculation of the recruits who joined the mine. These inoculations were very admirably organised, carried out, and recorded by Dr. J. C. A. Rigby, who was very ably assisted by Mr. Sheridan.

From January 21 onwards till March 15, 1912, every second native was inoculated as he arrived at the mine. From that date onwards only every third man was kept as a control, and gradually as it became more and more evident that good results were being obtained an increased proportion of the recruits were inoculated.

At the outset the dose which was employed was 200 million pneumococci; and gradually as it became clear, from the results that were coming in from Mass-experiment No. 5, that the employment of larger doses was indicated, the doses were gradually increased to 250 millions, then to 500 millions, until finally a dose of 1000 millions was reached.

Returns which were very carefully prepared were furnished to us every month, and we were further, at the end of the first six months, and again at the end of the first year of the experiment, furnished with a detailed synopsis of the results. These returns are our authority for the facts set forth below.

Table XIX

Showing the Results for the whole Native Population of the Mine for the Year beginning January 22, 1912, *and ending January* 21, 1913.

	Daily average strength of the group.	Cases of pneumonia.		Deaths from pneumonia.	
		Number.	Percentage.	Number.	Percentage.
Inoculated ..	9909 ..	508 ..	5·13 ..	154 ..	1·55
Uninoculated ..	4520 ..	467 ..	10·33 ..	145 ..	3·21

We subjoin also, for reasons that will presently appear, another statistical record which excludes all those who were on the mine on January 21, 1912, and takes into account all the natives who came to work on the mine during the next twelve months.

It may be remarked that the fact that the native at this mine usually works on a six months' contract would make the daily average population equivalent to about half the number of the natives who join in the year.

Table XX

Showing for the period January 22, 1912, *to January* 22, 1913, *the Results for the Natives who came in that year to work on the Mine.*

	Number of natives who joined the mine.	Cases of pneumonia.		Deaths from pneumonia.	
		Number.	Percentage.	Number.	Percentage.
Inoculated ..	17,431 ..	376 ..	2·16 ..	120 ..	0·7
Uninoculated ..	6,771 ..	348 ..	5·14 ..	120 ..	1·77

Finally, in connexion with the mass-experiment here in question, we may give the figures for the corresponding period relating to the incidence- and death-rate of "other diseases" in the inoculated and uninoculated sections of the population. These figures are as follows: *Inoculated*, average daily strength, 9909; incidence-rate, 47·2 per cent; death-rate, 0·93 per cent. *Uninoculated*, average daily strength, 4520; incidence-rate, 106·6 per cent; death-rate, 1·90 per cent.

SECTION V

GENERAL SURVEY OF THE RESULTS OBTAINED BY THERAPEUTIC AND PROPHYLACTIC INOCULATION OF PNEUMOCOCCUS VACCINE; AND CRITICAL COMMENT

VACCINE-THERAPY OF PNEUMONIA

In connexion with the vaccine-therapy of pneumonia we have, on the one hand, the fact that inoculation in the form of small doses frequently repeated was absolutely ineffective (Table XI); and, on the other hand, the fact that inoculation in the form of a single large dose, administered in the incubation period, often arrested the disease and averted death (Table XVIII).

That the difference of dose determined the difference of event, is to us as good as certain. Let us—recalling to mind the general propositions formulated in Section II—here take note of the fact that the doses which we found inoperative were doses from which there could, at best, have been expected that they should elicit a local immunising response. Further, let us note that the evocation of such response would be dependent upon a sufficiency of antigen passing into solution in the lymph at the seat of inoculation.

Lastly, let us note that it is quite likely that microbes which are ingested by phagocytes may, from the point of view of the immunising reaction, be left quite out of regard.[1] In connexion with this it is almost superfluous to point out that when comparatively small numbers of microbes are inoculated, and when they come into contact with a lymph which possesses opsonic power, but only inappreciable bacterioclastic power, they will almost certainly sooner or later be ingested by phagocytes.

[1] We hark back here to an objection which was long ago (as we think inappositely, because the blood-fluids exert a bacteriolytic effect on the cholera vibrio) brought forward by Metchnikoff in connexion with Ferran and Haffkine's anti-cholera inoculations.

In general contrast with all this would be what would happen when a large dose of vaccine is inoculated. In this case the microbes would be carried on into the main lymphatic current and blood-stream, with the result that inevitably some would escape phagocytosis, and inevitably some of these would, even if the blood had but very little bacterioclastic power, be broken down. And there would supervene upon the convection of the antigen to the tissues through the blood a systemic immunising response.

As we see no reason to suppose that the conditions appreciably alter, and as we know that the bacterioclastic power of the blood does not sensibly increase, when pneumonia develops, we think it reasonable to expect that the favourable results which were obtained by the inoculation of doses of 250 to 1000 millions of pneumococci would repeat themselves if this treatment were applied in the early stages of pneumonia. We were prevented from undertaking a therapeutic mass-experiment upon these lines in the season 1912–1913 by the fact that we were then engaged upon Mass-experiment No. 5 (that which furnished the data we have here been reviewing) and had to be on our guard against falsifying the results it was giving by any therapeutic interference.

PROPHYLACTIC INOCULATION AGAINST PNEUMONIA

The comparative statistics which have been set forth above testify, as has been seen, in every case to a reduction in the incidence-rate and death-rate of pneumonia in the inoculated.

In adjudicating upon a procedure of prophylactic inoculation the following general theses must be taken into account.

(1) The advantage derivable from a prophylactic inoculation will be limited by the patient's power of immunising response.

In accordance with this, one would not expect to

achieve as much by inoculation in a naturally non-resistant population—such as that represented by the Tropical Native Labourers on the Rand—as in a more resistant population—such as is, by common repute, represented by the Non-Tropical Native Labourers on the Premier Mine.

We may, perhaps, bring into relation with this consideration the fact that we have, as the result of the application of prophylactic inoculation to the Tropical Natives on the Rand, in *Mass-experiment No.* 1 (*Tables XII and XIII*) a reduction of 37·5 per cent in the death-rate of the inoculated upon an observation-period of six months; in *Mass-experiment No.* 3 (*Table XV*) a reduction of 31 per cent in the death-rate of the inoculated upon an observation-period of four months; and in *Mass-experiment No.* 5 (*Table XVII, Group E*) a maximum reduction of 50 per cent in the death-rate of the inoculated upon an observation-period of six months; while we have upon the Premier Mine (*Mass-experiment No.* 6, *Table XX*) upon a twelve months' observation-period a reduction of 60 per cent in the death-rate for the inoculated.

(2) The advantage derivable from prophylactic inoculation will depend upon the degree to which the population to which it is to be applied has already run the gauntlet of the particular microbic infection in question.

In accordance with this, one would expect greater advantage from inoculation when applied to a population newly arrived in the field of infection, than from inoculation applied to a population which had been long in such a field *continuously* exposed.

It falls in with this, that while we have in the inoculated in Mass-experiment No. 5, Group E—an experiment in which the uninoculated had an incidence-rate of 15 per cent, and a death-rate of 5 per cent over a five-month period—a reduction of 35 per cent in the incidence and of 55 per cent in the deaths; we have in the inoculated

in Mass-experiment No. 4[1]—an experiment in which the uninoculated had an incidence-rate of 3·4 per cent and a death-rate of 1·3 per cent for the same period—a reduction of only 10 per cent in the incidence-rate and of 34 per cent in the death-rate.

We may further note that we have, in connexion with Mass-experiment No. 6, in the case of the inoculated a reduction in the incidence-rate of 50 per cent, or 58 per cent ; and a reduction in the death-rate of 52 per cent, or 61 per cent ; according as we take as our controls (as in Table XIX) the population already on the mine, or (as in Table XX) the population of new arrivals.

(3) Where in comparative statistics we find that the difference between the inoculated and the uninoculated is after a certain time effaced, this does not necessarily indicate that the immunity of the inoculated is diminishing. We may be witnessing, instead of a descent of the inoculated to the level of the uninoculated, an ascent of the uninoculated to the level of the inoculated.

This is, presumably, the true interpretation of the fact that our inoculated natives displayed only for a comparatively short period an advantage over the uninoculated. For we have uniformly, in all our records (Mass-experiments Nos. 1, 3, and 5 ; Tables XII and XIII, XV and XVII), and therefore presumably independently of any change in the external conditions—instead of a progressive falling off in the incidence-rate and death-rate of pneumonia in the inoculated, a progressive improvement in the incidence and death-rate in the uninoculated.

The point of interest which here suggests itself is the question as to how the ascent of the uninoculated to a higher level of immunity, and the accompanying progressive improvement in the figures for the inoculated, which is a feature of all the statistics, is to be accounted

[1] In this mass-experiment the dose of vaccine employed was the same as that in Mass-experiment No. 5, Group E, and the culture medium employed in making the vaccine was also largely the same.

for. Two alternative hypotheses here suggest themselves. The attainment of a higher level of immunity may be explained by supposing that the most susceptible individuals have been weeded out by death from each group. But this is not a very acceptable hypothesis, for it is hard to believe that infection can ever be distributed over a population in so uniform a manner as punctually to pick out and kill all the more susceptible individuals. It is much more probable that the progressively increasing resistance in both the inoculated and uninoculated groups is achieved by processes of self-immunisation consequent upon minor infections which affect practically the whole mass of the population. We have what we think presumptive proof that such agencies are at work in the fact, already adverted to above, that there were, in practically every group of four to six uninoculated natives whom we employed as controls, some who were almost certainly suffering from minor pneumococcus infections.

Not only does this theory furnish, as it seems to us, a satisfactory explanation of the progressive improvement in the figures for both inoculated and uninoculated, but it puts into our hands, as we think, a clue which may guide us in our search for the optimum dose of a vaccine for prophylactic use. In the case where we institute a comparative experiment—and we have the results of such a comparative experiment set out in Table XVII, Groups A and E—*employing in* one group (let us call it *Group No.* 1) *a smaller*, and in another group (let us call it *Group No.* 2) *a larger dose ;* and where we then find that in *Group No.* 1 the figures taken, when those for the uninoculated become equally good, are inferior to those afterwards reached ; and that in *Group No.* 2 the figures, taken again when those for the uninoculated become equally good, are not afterwards improved upon—we may legitimately infer that in *Group No.* 1 prophylactic inoculation left something undone which was afterwards achieved by self-immunisation ; and that in *Group No.* 2

prophylactic inoculation accomplished, so far as appears, all that self-immunisation was capable of achieving.

It will be realised that this amounts to saying that the optimum dose, or series of doses, of vaccine is that which produces an immunising response which is incapable of any further reinforcement ; and that we ought to aim at effecting by prophylactic inoculation all that living in the presence of infection, and having actual dealings with infection, is capable of achieving.

(4) Comparative statistics furnish only a very incomplete account of the profit earned by any successful prophylactic inoculation. It has among statisticians been too much the habit to give credit only for the profit shown upon comparative statistics, and to disallow credit for maintained advantage unless proof is produced that the incidence and death-rates of the disease have been, as the ordinary statistician would wish, maintained in the uninoculated section of the population.

Examples of this method of auditing proofs are furnished by the fact that when, in connexion with small-pox vaccination, the statistical records for France, which is very incompletely, and Germany, which is very completely vaccinated, are contrasted ; or when, in connexion with typhoid inoculation, the condition in the Army in India before typhoid inoculation, is contrasted with its condition to-day, when the large bulk of the British troops are inoculated ; or when, in connexion with that same process, a comparison is made between the statistics for the Jacksonville Camp in the Spanish-American War, where out of a strength of nearly 11,000 U.S. troops, all being uninoculated, at least 1729 contracted typhoid, and the statistics for the San Antonio Camp on the infected Mexican frontier where nearly 13,000 U.S. troops, who were all inoculated, were massed with only one case of typhoid[1]; the comparison is in each case

[1] Russell, United States Army Medical Department, Bulletin No. 2, January, 1913, p. 11.

disallowed on the ground that there were not sufficient uninoculated controls interspersed among the inoculated, or that the contrasted populations were not quite homologous, or that the conditions to which they were exposed were not exactly alike.

The statistical auditor, who refuses to give any credit upon vouchers which have been left in some point incomplete, is of course keeping himself well within the law. But he is leaving quite out of regard the equities.

When the question as to how we should evaluate the results of an effective inoculation process (and we may here deal specifically with pneumococcus inoculation) is regarded from this point of view—in other words, when we take a broad view of the probabilities—it will become clear that it would be altogether proper to claim credit :— *in connexion with the inoculated :* (*a*) for any diminished incidence and any diminished death-rate from pneumonia which is attested by comparative statistics for inoculated and uninoculated ; (*b*) for any diminished incidence and death-rate from other pneumococcic infections (whether diagnosed as such, or undiagnosed) which comes upon the record ; and (*c*) for any diminished incidence and death-rate from infections which were not due to the pneumococcus, but were directly consequent upon pneumococcic infection.

Further, *in connexion with the uninoculated* section of the community, credit may equitably be claimed (*d*) for any diminution in the incidence-rate and the case-mortality of pneumococcic infections—for the former, because a reduction in the number of pneumococcic cases in the inoculated would diminish the general volume of infection ; for the latter, because a reduction in the virulence of the infection might reasonably be expected from the diminished ' passaging ' (i.e. transference from case to case) of the infective microbe.

It is to be noted that it is only the establishment of the general principle that we may anticipate profits under

each of these headings, and that these profits cannot equitably be left out of account, which is here vital. The matter of real concern in connexion with any effective inoculation procedure is that by it we are transported out of a vicious circle—a *circulus vitiosus* of infection and non-resistance, into a 'propitious circle'—a *circulus felix* of increased resistance and diminished infection.

In comparison with the establishment of this, it is a small matter that, when fairly entered upon a propitious circle, it becomes impossible to tell how much of the sum-total of effects is due to inoculation, and how much to other causes.

With these preliminary explanations and reserves, we may here subjoin a further table which has reference to the mass-experiment on the Premier Mine.

Table XXI

Showing for the whole Native Population of the Premier Mine the Incidence and Death-Rate for Pneumonia; the Incidence and Death-Rate for "Other Diseases"; and also the number of Working Days lost through illness; for the months February to May, in* 1911, 1912, *and* 1913 *respectively.*

	1911.	1912.	1913.
Population (daily average strength) ..	10,426	12,549	15,284
Proportion of the population inoculated ..	0	About 50 per cent	About 92 per cent
Incidence-rate of pneumonia	4 per cent	1·28 per cent†	0·74 per cent†
Death-rate from pneumonia	0·97 per cent	0·31 per cent	0·14 per cent
Incidence-rate of other diseases	31 per cent	20·7 per cent	14·4 per cent
Death-rate from other diseases	0·51 per cent	0·38 per cent	0·34 per cent
Number of working days lost per hundred native labourers ..	275	177	131

* We have been furnished with data for this comparison only up to May, 1913.

† In 1912 the incidence-rate was 0·86 per cent for the inoculated and 1·7 per cent for the uninoculated. In 1913 it was 0·6 per cent for the inoculated and 3 per cent for the controls.

SECTION VI

CONCLUDING CONSIDERATIONS, AND RECOMMENDATIONS WITH REGARD TO THE MEASURES TO BE TAKEN TO COMBAT THE PNEUMONIA ON THE RAND

In considering what measures ought to be taken to combat the pneumonia on the Rand it is essential to start with a proper appreciation of the character and natural history of the disease.

The salient facts, in connexion with the pneumonia which affects the native labourers on the Rand, are as follows :—

The disease is—as investigation, and in particular the investigation made by Dr. Turner in Tropical Africa, has shown—unknown, or practically unknown, in the native kraals.

The disease has no special relation to the mining work on the Rand. It takes no heavier toll of the natives at work in the deep level mines of the Rand than of those employed on the Premier Mines on open workings. Moreover the disease is seen at its very worst in the compound of the W.N.L.A. among the newly arrived natives who have not yet begun their work on the mines.

Again, the prevalence of pneumonia and other pneumococcic infections among the natives in the mines of the Transvaal can have no special relation to its climate or to its elevation above the sea-level ; for these infections caused a very heavy mortality among the African natives working upon the Panama Canal at sea-level. And they also cause very serious loss of life among the negro labourers and soldiers in Rhodesia, the French African Colonies, the Egyptian Soudan and elsewhere.

Finally we have the very material fact, which has been brought out in this Report, that the blood of the African native is, so far as relates to its power of phagocytosing

and killing the pneumococcus, very inferior to that of the European, and that the capacity for immunising response is also much less in the African than in the European.

These considerations make it practically certain that the prevalence of pneumonia on the Rand is to be ascribed to the bringing together into close contact in compounds of a population which has, as a racial character, a low resisting power to the pneumococcus.

If this is so, it is obviously a circumstance which ought to dictate our plan of attack, and to determine in particular what place in our scheme of operations ought to be taken respectively (*a*) by measures which aim at preventing the convection of pneumonia from man to man ; (*b*) by measures which aim at holding off influences which might impair the natives' resistance to infection ; and (*c*) by measures which aim at increasing the natives' resistance to infection.

(*a*) Under the heading of " measures for avoiding the convection of infection from man to man " would come : measures for the earliest possible detection and isolation of cases of pneumonia ; measures for the disinfection of the sleeping quarters from which such cases have been removed ; measures for diluting the infective matter in these sleeping quarters by schemes of ventilation ; and, lastly, measures for the quarantining of recovered pneumonic patients with a view to the prevention of a spread of infection from these.

With regard to these, we may remark that, while we see no reason to doubt that each of these measures would in its degree counteract the spread of infection, we have grave doubts as to whether they could ever be made effective measures for combating pneumonia on the Rand. We are taking into consideration here, *first*, the fact that it would be a very difficult thing to carry out upon the Rand measures for the early detection and subsequent quarantining of pneumonic cases ; *secondly*, the fact that we have on the Rand not only to deal with

pneumonia but also with very numerous cases of lighter forms of pneumococcic infection; and, *thirdly*, the fact that the pneumococcus lives saprophytically on the mucous membrane of a majority of healthy men.

Moreover, in connexion with the question of the adoption of measures for preventing the spread of pneumonic infection from man to man, it will be well never to leave out of sight the fact that given a population which, like a European population, possesses a relatively high resistance to the pneumococcus, all such measures can be dispensed with.

(*b*) Coming now to "measures for holding off influences which might impair the Native's normal resistance to infection"—and we have in view here such a measure as the provision of 'change-houses'[1] for safeguarding the native against chills—we are of opinion that the place of such measures in a plan of campaign against pneumonia is at best a very subordinate one. In this connexion we would again emphasise that the really predisposing moment in the case of pneumonia is to be found, not in those incidental and temporary impairments of resisting power which may occur in connexion with mining work, but in that abiding defect of resisting power which is normal to the native.

We have here clearly a fact which dictates recourse to inoculation, and which indicates that a very important place in our scheme of operations ought to be assigned to this measure.

(*c*) Our recommendations in connexion with inoculation are as follows:—

We recommend that prophylactic inoculation should, except only in the case where a mass-experiment is being undertaken, be applied as a routine measure to every native on recruitment.

[1] It may be explained that 'change-houses' are sheds in which the native is compelled to change his clothes before he emerges from the mine into the open air.

In the light of the results furnished by Mass-experiment No. 5 (Table XVII, *supra*), we suggest that a dose of 1000 millions of pneumococci cultivated upon glucose blood broth might appropriately be employed as the ordinary prophylactic dose.

Further, in view of the results obtained in Mass-experiment No. 4, Table XVI, we recommend that the natives should be reinoculated after the expiration of four months, and that here again a dose of 1000 millions of pneumococci should be employed.

We would not for the present advise any general application of therapeutic inoculation. We would, however, urgently recommend that it should be made the subject of further investigation.

We regard the continued prosecution of research in connexion with inoculation as essential to the attainment of the best results.

We recommend that such research should comprise, on the one hand, the institution of properly controlled mass-experiments, and on the other hand, the systematic measurement of the protective substances produced in response to inoculation. In such measurements we suggest that the method for measuring the phagocyto-bactericidal power of the blood which is described in this Report, or some modification of that method, should be utilised.

In connexion with prophylactic inoculation, the task of research should be to obtain confirmation of the conclusion that we have in 1000 millions the optimum dose for prophylactic purposes. It would also be well to make certain that reinoculation after a period of four months is really required.

In connexion with therapeutic inoculation, the first task of research should, we think, be to institute a mass-experiment in which one large dose of vaccine should be given to the patient at the outset of his pneumonia attack. We suggest that a dose of 500 millions might be tentatively

employed in such an experiment, and we think that in such an experiment every alternate patient should be taken for a control.

In concluding this Report we desire again to express our obligations to Dr. George A. Turner, the medical officer in charge of the Witwatersrand Native Labour Association Hospital, Johannesburg, for unwearying assistance in connexion with the inoculations which we carried out in his hospital and on the Rand, and to Dr. F. C. Lister, Dr. A. R. Friel, and Mr. G. Friel for valuable help in our laboratory work. We desire also to thank Mr. P. Ross Frames, Chairman of the Research Committee, and Managing Director of the Premier Mine, for the helpful assistance he afforded us in both of these capacities. And to Dr. J. C. A. Rigby and to Mr. H. P. Sheridan we owe a very special debt of thanks for their eminently successful achievement—the mass-experiment carried out on the Premier Mine.

Finally, the author of this Report desires to express to Dr. W. Parry Morgan, who took independent charge of the Inoculation Work after March, 1912, his grateful acknowledgments for his initiative and forethought in planning Mass-experiments Nos. 3, 4, and 5, and for the solicitude with which he carried these out. In connexion with our work acknowledgments are also due to the excellent and conscientious labours of Mr. O. Slawkowsky, our chief laboratory assistant, and of Mr. P. Hardwick, our statistical clerk.

APPENDIX No. I

Synopsis of the more recent observations relating to æthylhydrocupreinhydrochlorate (Optochin), and its employment in the treatment of pneumococcus infections.

THE recent literature dealing with laboratory experiments with 'optochin' and its therapeutic application in connexion with pneumococcus infections may be summarised as follows :—

(*a*) *Laboratory experiments.*—The results of our *in vitro* experiments with optochin, and in particular the observations that this drug exerts its bactericidal action specifically upon the pneumococcus, and that it is operative in very high dilutions and in serum as well as in watery solution, have been confirmed by SCHIEMANN and ISHIWARA[1] (working in Neufeld's Laboratory); by MORGENROTH and BUMKE[2]; by TUGENDREICH and RUSSO[3] (working in Morgenroth's Laboratory); and by RUSSO.[4]

(*b*) *Local Application of Optochin as a Disinfectant in Pneumococcus Infections.*—A considerable number of oculists have published excellent results obtained by the local application of optochin in pneumococcal affections of the conjunctiva and cornea (*ulcus serpens*).

(*c*) *Effect of the administration of Optochin in Pneumonia.*—Three authors—VETLESEN,[5] and LENNE,[6] who employed the drug respectively in 9 and 17 cases (Europeans), and VON BAERMANN,[7] who employed the drug in 31 cases (Dutch East India Natives)—have published their experience. All of them seem to have been favourably impressed.

[1] *Zeitschrift f. Hygiene, Bd.* 77, *Heft* 1, 1914.
[2] *Deutsche Medicinische Wochenschrift*, 1914, No. 11.
[3] *Zeitschrift f. Immunitatsforschung, Bd.* 19, *Heft* 2, 1913.
[4] *Annali d'Igiene sperimentale, Bd.* 23, *Heft* 4, 1913.
[5] *Berliner Klinische Wochenschrift*, 1913, Nr. 32.
[6] *Berliner Klinische Wochenschrift*, 1913, Nr. 43.
[7] *Zeitschrift f. Experimentelle Pathologie u. Therapie, Bd.* 15, 1914.

(*d*) *Question of Risk to Eyesight.*—Vetlesen, who employed 0·5 gramme t.i.d., did not observe any ocular symptoms. Lenne had one case of amaurosis among his 17—the trouble rapidly disappearing when administration of the drug was suspended. Von Baermann observed no optical troubles in his 31 cases (1·5 gramme was administered daily). Izar and Nicosia,[1] who employed optochin in similar quantities in the treatment of malaria, saw only one case of amaurosis, and again in this case the disturbance passed off when the drug was discontinued. Morgenroth[2] reports 4 cases of pneumonia in which 3 grammes of optochin was administered in the course of the day. Three of these patients (they were cases where the temperature came down critically) developed amblyopia, but this also passed away rapidly.

Thus the only case of optochin amaurosis which is not known to have recovered is one of the two cases which came under our observation in South Africa, and who shortly afterwards passed out of our ken.

In view of the fact that these later data show that there is, provided moderate doses of optochin are employed, no appreciable risk of serious eye complications, it would seem imperative to experiment further with optochin in pneumonia, even in view of the fact that we have of course no guarantee that the optochin will find access to the microbes which are lying outside the blood-vessels in the consolidated lung

[1] *Berliner Klinische Wochenschrift*, 1914, Nos. 9 and 10.
[2] Personal communication.

APPENDIX No. II

Return showing the Incidence- and Death-rate from Pneumonia and other Medical Diseases on the Premier Mine for the period January 1st, 1908, to December 31st, 1913.

(To be read in association with the History of the Preventive Inoculations against Pneumonia on the Premier Mine, pp. 101–102 and 104–110 *supra*).

Year.	Daily average strength of native labourers.	Incidence-rate per Thousand.		Death-rate per Thousand.		Case Mortality per Cent.	
		Pneumonia.	Other Medical Diseases.	Pneumonia.	Other Medical Diseases.	Pneumonia.	Other Medical Diseases.
1908...	7,906	70·71	442·95	14·17	7·84	20·04	1·77
1909...	7,790	104·88	603·21	17·97	5·26	17·14	0·87
1910...	11,287	153·54	658·10	28·97	13·20	18·87	2·01
1911...	10,800	128·98	888·15	26·94	13·80	20·89	1·55
1912...	14,125	67·68	665·27	19·96	13·38	29·50	2·01
1913...	14,172	31·75	480·74	4·80	8·82	15·11	1·83

Return showing the Incidence- and Death-rate from Pneumonia and other Medical Diseases on the Premier Mine for the four months, January to April inclusive, during the years 1908 to 1914.

Year.	Daily average strength.	Death-rate per Annum per Thousand of Population.		Case Mortality per Cent.	
		Pneumonia.	Other Medical Diseases.	Pneumonia.	Other Medical Diseases.
1908.....	7,856	12·22	11·07	34·41	4·01
1909.....	7,708	5·84	3·11	19·23	0·69
1910.....	11,915	19·64	12·34	18·66	2·24
1911.....	10,375	32·96	19·66	21·15	1·98
1912.....	11,257	6·93	10·39	16·76	1·42
1913.....	14,912	3·82	8·45	15·57	1·79
1914.....	13,201	2·27	15·00*	15·63	3·41

* The increased sickness amongst the Natives (other Medical Diseases) in January, 1914, is accounted for by an epidemic of Typhoid, which broke out in the early part of the month.

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